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CLINIC OF DR. ROBERT T. FRANK

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HORMONE THERAPY IN WOMEN

"HORMONAL THERAPY" for women has reached scandalous proportions. Women not only know that endocrine remedies are available and are employed, but in many instances insist that they be given "glandular medicines," no matter how absurd the use of such medication may be in their particular case.

In spite of notable exceptions, the medical profession as a whole is woefully ignorant of the application, limitations and value of such therapy and too often weakly panders to the clamorous demands of its clientele. Moreover, hypodermic injections are almost universally resorted to when potent products, readily absorbed through the gastro-intestinal tract, could be substituted. On the other hand, not infrequently products which are completely inert by oral exhibition, such as gonadotropic factors and androgens, are given by mouth, or inert desiccates, of which a large number are still on the market, are prescribed where potent remedies are indicated.

One of the main causes of this chaotic and unsavory situation is the attempt by some clinicians to apply prematurely to humans every result of laboratory experimentation, and the equally premature and too often inaccurate popularization in the lay press of speculative and spectacular medical presentations.

These critical remarks do not signify that hormonal therapy is valueless. On the contrary, brilliant advances have been made in this and the allied field of vitamins.

THYROID

One of the most valuable endocrine products is the first one discovered, namely thyroid substance. When the basal metabolism is lowered, as determined by a metabolism test, desiccated thyroid substance is indicated. The dosage should be determined by the basal metabolism reading and the tolerance shown by the individual patient. The indications for thyroid medication encountered by the gynecologist and obstetrician mainly are the following:

Indications.—A large group of adolescents suffer from *delayed onset of the menses* or, after the menarche is established, become *amenorrheic.* If there is thyroid deficiency (basal metabolic rate from —15 to —25 per cent) a quick response to desiccated thyroid, in doses of 2 to 5 grains daily, may be anticipated.

Case I. Eunuchoidism, Adolescent Goiter, Hypothyroidism, Amenorrhea.—Z. B. was seen at eighteen years of age. Onset of menses had been at thirteen years, and they occurred every twenty-seven to twenty-nine days for three to four days. At fifteen years she developed goiter; at sixteen years, amenorrhea which had persisted for two years when first seen.

Tall, blond, slightly eunuchoid build; 5 feet, 6¾ inches tall, 117 pounds in weight; secondary sex characters feminine, well developed; uterus very hypoplastic; adnexae normal; virginal introitus; basal metabolic rate —14 per cent.

The patient was treated in Canada and Vienna for long periods of time, by "injections" and by "stimulating *x*-ray doses to the pituitary." At the age of twenty-five she moved to New York City permanently.

When seen by me the patient had not menstruated for two years. She was put on thyroid substance, 1½ grains daily, for three weeks, with a free period of one week. This type of therapy was continued for some time. Under this treatment the basal metabolic rate was kept at +5 to +6 per cent. In six months she began to menstruate every six to seven weeks. After one and one-half years, menses failed to appear. A pregnancy test was positive. The patient was delivered at term. After this, menstruation did not return in spite of therapy, until three years later, and is still irregular.

This is an unusually stubborn case of hypothyroidism, complicated by eunuchoidism. In the average case, particularly if the basal metabolic rate is found to be —15 to —25, the results appear earlier and the effect is more striking.

A considerable, though smaller, group of adolescents with *excessive bleeding* (both menorrhagia and metrorrhagia) is

encountered. Alarming anemia may develop (hemoglobin down to 20 to 35 per cent, necessitating transfusion). Of these patients, I have found about 15 per cent who are hypothyroid and who respond at once to thyroid therapy. Only a small number of adults with amenorrhea are hypothyroid.

Case II. Puberty, Menorrhagia and Metrorrhagia.—M. C., aged sixteen years, began to menstruate at thirteen years. She had been born prematurely, her birth weight being 4 pounds. Her childhood had been normal for over a year after onset of the menarche, she had menstruated every twenty to twenty-two days, bleeding moderately for three days, followed by three days of staining. At the age of fourteen, she bled profusely for three weeks, with hemoglobin down to 35 per cent; she was transfused and given a prolonged series of antuitrin-S injections. In the following two years, the patient had four attacks of severe menorrhagia. Recently there has been a period of amenorrhea of four months.

When seen by me, the patient had been bleeding moderately for ten days. The hemoglobin was 70 per cent. The general physical examination showed a small, gracile, attractive young girl, 5 feet in height, weight 103 pounds, with fully feminine characteristics. The uterus and adnexae were normal. Hemoglobin was 70 per cent, the blood count otherwise being normal, as was bleeding and clotting time.

The patient was given pregneninolone (a progesterone preparation) by mouth, 10 mg. daily, with no relief. In two weeks the hemoglobin dropped to 48 per cent as the bleeding continued. She was therefore transfused. The basal metabolic rate was determined at —18 to —20 per cent, three determinations being made on successive days. Because of the patient's small size and low weight, only 2 grains of desiccated thyroid were given each day. The patient has since remained well and menstruates normally.

Few *obese* females, unfortunately, are hypothyroid. The majority of fat women have a normal metabolism, and many tolerate thyroid substance badly. In my experience, the vast majority of cases of obesity are due to overeating in spite of vehement denial by the patient (amount, selection of foods).

It is well to remember that at the onset of any serious glandular disturbance—pituitary, thyroid, adrenal especially —menstrual disturbances (bleeding as well as amenorrhea) are the rule. Consequently, some of these patients consult the gynecologist because of the menstrual disturbance. At this early stage, the incipient endocrine disease readily is overlooked and wrong therapy is resorted to.

Case III. Anorexia Nervosa.—M. H., aged seventeen years, menstruated at thirteen and one-half years. Her menses have been irregular, occurring every five to seven weeks; she has not menstruated for six months. She had weighed 140 pounds, but by dieting she reduced to 120 pounds.

General physical findings were normal; the patient was fully feminine; height 5 feet, 4¼ inches; hemoglobin 80 per cent. Pelvic examination showed normal internal genitalia. The patient was advised to stop dieting and was not seen for some time thereafter.

The patient did not menstruate for the next year. Her loss of weight continued downward to 105 pounds. This young woman was markedly introvert and although she apparently got along well with her family, many mental conflicts existed. The following year her weight had fallen to 85 pounds. She had been admitted to a hospital for observation, where, because of the malnutrition, the very low basal metabolism, extremely low blood pressure and asthenia, a diagnosis of Simmonds' disease was arrived at, and she was given injections of a specially prepared anterior pituitary extract. No improvement followed.

I again saw this patient two years after the first visit. A careful history convinced me that this was a case of anorexia nervosa. The examination showed a markedly asthenic, underweight, listless young woman whose basal metabolic rate was —33 per cent. I insisted upon complete separation from the family, country rest and quiet, a roborant diet, with emphasis on the protein factor, and then gave her 3 grains of thyroid daily. The weight gradually improved, the patient's vigor increased, the menses returned. Without thyroid medication, the basal metabolic rate was found to be —13 per cent. Six months later, it was normal. She has now remained well for five years.

ESTROGENS

Estrogens are widely and injudiciously prescribed, often without rhyme or reason. Comparing the available compounds on the basis of biologic activity, estrone 1/10,000 mg., estradiol 1/100,000 mg., and estriol 1/1000 mg. exert approximately the same effect. Some preparations are absorbed only subcutaneously, others by mouth. Response to cutaneous application is increased, but rate and amount of absorption is difficult to control.

Indications.—Indications for estrogen therapy are clear-cut and limited. In *infantile* and *prepuberal gonorrhea*, estrogens (by vaginal suppository, by mouth or by hypodermic) thicken and keratinize the vaginal mucosa, rendering it more resistant to the gonococcus. Simultaneous local and general chemotherapy should be instituted.

The main indications for estrogens, however, are *in the menopause*—physiological, *x*-ray and surgical castration; flushes and sweats, intestinal symptoms, arthralgias, senile vaginitis, headache and psychical unrest may be relieved. Some involutional psychoses are completely relieved during treatment. As the therapy must be given over protracted periods, *oral* medication should be resorted to. The intervals

between treatments (three to four weeks), should be increased progressively.

Case IV. Menopause.—A. M., aged forty-nine years, has experienced no menstruation for five months; there are frequent flushes, especially at night, accompanied by sweats, palpitation and dyspnea. Marked nervousness, indigestion and fatigue are present.

The findings of the general examination are normal; parous introitus; involuted uterus in anteflexion; adnexae normal; blood pressure 140/90.

The diagnosis was that of beginning menopause. The patient was given tablets of estradiol, ½ mg. each, twice daily. In the subsequent months, three courses of this medication, each for thirty days, with intervals, first of one week, later of two weeks, were given. Nervousness greatly diminished and there were no flushes; indigestion was relieved.

This patient has been seen at six-months' intervals for the last four years. Unless she takes estrogens, there is annoying return of the flushes and sweats. At times as much as 1½ mg. a day must be taken to abolish the symptoms. This patient, as have a number of others, has noted that when she takes 1½ mg. of estradiol benzoate a day, and then stops the medication abruptly, within a week a vaginal bleeding results. For this reason she tapers off, first reducing the dose to ½ mg. a day, and then taking ½ mg. every other day. This avoids the bleeding. The patient's response to synthetic estrogen is equally good. This is a case of long-continued menopausal symptoms.

Contraindications.—*Amenorrhea* is neither improved nor cured by estrogens. A single bleeding may be induced by sufficiently large doses but no "regulation of menstruation" results. As many amenorrheas are of short duration, return of menstruation, falsely, is ascribed to the medication. Amenorrhea due to obesity, malnutrition or wasting disease (especially tuberculosis) should be treated according to indications.

Estrogens are contraindicated in excessive bleeding. They are useless, I have found, in hirsutism, dysmenorrhea, juvenile gigantism, acne and painful breasts.

Kraurosis vulvae, a "precancerous" disease, should not be treated with estrogen. Excision is indicated.

PROGESTIN

The corpus luteum hormones have limited indications. The results obtained are not readily evaluable or clear-cut, but so far are encouraging. Available is material for hypodermic injection and now a compound related to testosterone but with only infinitesmal and therefore negligible masculinizing properties, for oral use. Doses of less than 5 or 10 mg. are valueless. The price is unduly high.

Indications.—Indications are mainly *threatened* or *habitual abortion,* for not only is the corpus luteum secretion a powerful uterine relaxant, but this hormone is essential to embedding of the ovum. In *menorrhagia* and *dysmenorrhea,* some relief is noted, but I am unwilling from my observations as yet to attempt to pass a final opinion.

HORMONES OF DOUBTFUL VALUE

Androgens.—These, in my opinion, are *contraindicated* in the female, even though, in large doses, temporary atrophy or involution of the uterine lining can be obtained. The danger of producing hoarsening of the voice, enlargement of the clitoris, and abnormal hair growth is too serious to be ignored. On the other hand, androgens proved ineffective in curing alopecia (in both males and females) and gynecomastia in the male.

Gonadotropic Preparations.—Such preparations have proved most unsatisfactory. The so-called *urinary gonadotropins* (from pregnancy urine) enjoyed a great and quite undeserved vogue in the treatment of abnormal uterine bleeding.

Indications.—Their sole use is in aiding descent of the testes in adolescents, in which there is a response in possibly 25 per cent of patients. Use of the serum of pregnant mares, likewise has proved disillusioning. I have been unable to relieve amenorrhea or to produce ovulation in the human. Moreover, intravenous injection is required and the danger of causing serious anaphylactic shock must be guarded against.

Pituitary Growth Hormones.—In spite of prolonged trial on many patients, I have been unable to convince myself that any pituitary growth hormones, so far available, produce any effect whatsoever in the human. Any growth or development which occurred in the course of the one to two years of treatment could be ascribed to natural causes, as shown by stopping therapy or by the improvement in many untreated controls.

OTHER HORMONES

Other hormones, such as parathyroid hormone, insulin, adrenal cortical extract and desoxycorticosterone, pituitrin and adrenalin, have clear-cut indications irrespective of the sex

of the patient and therefore are not germane to the present exposition.

CONCLUSION

It is high time that much of the chaff be shaken out of endocrinology. There is so much of real value that the inert filler will not be missed, and the remaining potency will be heightened.

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VITAMINS AND PREGNANCY

ACCESSORY food factors, or vitamins, are necessary for proper nutrition, as well as for the prevention of deficiency diseases. It has been said that a healthy, normal individual never develops avitaminosis on an adequate diet. However, *subclinical* deficiency may occur because of faulty preparation of foods, poor eating habits or faulty assimilation, or because of increased requirements.

Nutritionists have long recognized that the calculated vitamin intake of foods in the raw state is never achieved because of reduction during cooking. The temperature of the water, its alkalinity, as well as the state of preservation of the food itself, are of great importance in this regard. Further decrease takes place when the fluid, or "potlikker," which contains large quantities of the water-soluble vitamins, is discarded. The poorer classes in the South, on a diet of corn bread and salt pork, drink "potlikker" to great advantage. The practice of frying foods may also reduce the amount of available vitamins. It can therefore be said that the supplementary use of vitamin preparations, even by healthy individuals on a normal diet, may be considered necessary under certain circumstances. If this supposition is correct for nonpregnant individuals, it has even greater significance in pregnancy because of the increased requirements.

Many important historical and experimental features in the vitamin literature must be passed by when we limit our discussion to pregnancy. At the same time it must be remembered that the available data contain certain discrepancies because of medical interpretations made by doctors of philosophy, and scientific interpretations by doctors of medicine;

as obstetricians, we must seek a middle course. Clinical application of information gained experimentally is difficult because tests for vitamin saturation in blood and urine are not known, or are not available generally. While it has not been difficult to study the effects of avitaminosis and hypervitaminosis in chicks, rats, rabbits and guinea-pigs by direct assay of the tissues, most of the knowledge regarding avitaminosis in the human has been obtained by studying patients with deficiency diseases, many of whom never become pregnant with the exception of those with healed rickets and osteomalacia. Therefore, knowledge of the role of the vitamins in pregnancy must be fragmentary at times and limited to the subclinical states and to animal experimentation.

The vitamin requirements during pregnancy will be discussed from three points of view:

1. Sterility, fertility and abortion.
2. Antepartum maternal (and fetal) requirements.
3. Puerperal and neonatal requirements of the mother (for lactation) and the nursing infant.

STERILITY, FERTILITY AND ABORTION

Vitamin E.—In the male, avitaminosis E causes degeneration of the germinal epithelium of the testis. This leads to nonviability of the sperm and sterility and, according to Mason, is also associated in some way with deficiency in vitamin A. Sterility in the male may be irreparable while, in the female, no degeneration of the ova occurs although infertility may result. The infertility of cows responds to the administration of vitamin E, as shown by Vogt-Moller who treated fifty sterile but otherwise normal animals, thirty-three of them becoming pregnant. Evans states that once pregnancy has occurred, the fetal structures are in need of vitamin E in order to prevent their absorption. This belief has created a widespread usage of vitamin E in the treatment of habitual abortion in the human with varying degrees of success. Vogt-Moller treated seventy-two women with histories of repeated abortions, using 3 gm. of wheat germ oil daily, and obtained fifty-five living children. Watson and Tew report similar results in thirty-four out of forty-six cases, and Currie had success in twenty-three out of twenty-four cases. However,

instances of term gestation are not uncommon after three or more abortions without specific therapy.

Vitamin E is available in wheat germ oil, lettuce, watercress and spinach, and its synthetic preparation is *alpha tocopherol*. Feiser has pointed out a chemical relationship between vitamins E and K.

Vitamin K.—Singleton has used vitamin K in the form of dehydrated young grass in fifteen cases in which patients had one or more abortions; eleven of these patients continued with the pregnancy. Three of his patients were habitual aborters; two of these women were carried to term.

Vitamin K is utilized by the liver for the formation of prothrombin, which is required for blood coagulation. It is conceivable that improper clotting at the time of implantation of the trophoblast may result in abortion. We have under our observation six patients who have had three or more abortions; four of these had a normal plasma prothrombin concentration while two were low, 60 and 66 per cent of normal, respectively, and therefore presumed to be deficient in vitamin K. One of these patients with four previous abortions became pregnant while receiving vitamin K, which raised the prothrombin level to 100 per cent of normal, but she promptly aborted.

ANTEPARTUM MATERNAL AND FETAL VITAMIN REQUIREMENTS

After pregnancy has been established, certain changes occur in the maternal organism which call for an increased vitamin intake. These changes include: an average weight increase of 24 per cent, an average increase in the basal metabolic rate to +16 per cent, hydremia, and the growing protoplasmic mass of the fetus whose needs must be met by the passage of adequate amounts through the placenta. Complicated situations arise when nausea and vomiting, dietary aberrations, anemia and toxemia develop; while other medical complications of pregnancy, including hyperthyroidism, tuberculosis, pneumonia and pyelitis, create increased requirements beyond the normal need for gestation.

Vitamin E.—The need for vitamin E after the threat of miscarriage is past is not conclusive. However, it may play a role in preventing stillbirths since Schiappa reports an increase

in the size of litters in animals and fewer intra-uterine deaths when E has been employed. In *abruptio placentae* Shute has prevented advancing detachment with massive doses of vitamin E. We have studied three cases of premature separation of the placenta with a view towards using vitamin K in the treatment thereof, but the prothrombin levels were normal in all of the cases.

Vitamin K.—Vitamin K is available as synthetic 2-methyl-1,4-naphthoquinone in corn oil, and this preparation is nearly a third more potent than the actual vitamin K concentrate. It is also available in aqueous solution as 2-methyl-1,4-naphthoquinone-3-sodium sulfonate. The dose is 2 mg. intramuscularly or orally with bile salts. Evidence points to the liver as the depot of utilization of vitamin K, where it is used to make prothrombin. This has been proved by Andrus and co-workers following total hepatectomy in dogs, as well as by liver destruction following chloroform poisoning. The prothrombin concentration of blood plasma may be a measure of vitamin K deficiency or sufficiency in the absence of disease of the liver and biliary tract.

Vitamin K is to be found in spinach, cabbage, cauliflower and soy beans, as well as in other vegetables, and insufficiency is unlikely when proper diets are employed. However, nutritional deficiency of vitamin K has been reported by Kark and Lozher in four nonpregnant patients who had diets deficient in fruits and vegetables. In a study of prothrombin concentration of seventy-five patients in various stages of pregnancy in our laboratory, six patients were found to have a level below 70 per cent and therefore were deficient in vitamin K. Two of these must be excluded because of pre-eclampsia and eclampsia, with probable liver changes. It is conceivable that vitamin K will serve as a test of liver function, particularly in the toxemias of pregnancy. In one of our cases with eclampsia the prothrombin was only 62 per cent of normal; 4 mg. of vitamin K given parenterally failed to raise it, indicating impaired function of the liver.

The placenta is not a barrier to the passage of vitamin K, since administration during pregnancy and labor increases the prothrombin concentration of the cord blood to three times the usual amount, according to Hellman and Shettles; others

have made similar observations. This has resulted in the widespread administration of vitamin K to pregnant women as a prophylactic agent against *hemorrhagic disease of the newborn*. This disease has been found to be associated with a marked hypoprothrombinemia which may be regarded as physiologic since it is present in all newborn infants, as shown by Brinkhous, Smith and Warner. They found an average prothrombin concentration of 26 per cent of normal in the cord blood of eight infants. We have corroborated this finding in a study of forty-two infants who had an average of 23 per cent of normal. Several infants had levels as low as 5 to 10 per cent without development of hemorrhagic diathesis. Javert and Moore have postulated that the hypoprothrombinemia of the newborn is due to liver insufficiency on the basis of a patent ductus venosus. Despite the low concentration in the infants, they have a normal rate of convertibility of prothrombin to thrombin as shown by Owen and his coworkers, which probably explains the low incidence of hemorrhagic disease which in the New York Lying-in Hospital is only 0.7 per cent. This incidence is in agreement with that of Townsend published in 1894.

Whether antepartum administration of vitamin K will reduce the incidence and mortality rate of hemorrhagic disease remains to be seen. At least 10,000 cases must be studied before definite conclusions can be drawn. In the meantime there are other important etiologic factors, such as the trauma of labor. We are of the opinion that uterine contractions produce capillary endothelial asthenia and rhexis, which results in generalized multiple hemorrhages and ecchymoses. These hemorrhages may be regarded as physiologic. They reach pathologic proportions when the clotting mechanism is abnormal; *i.e.*, hypoprothrombinemia. However, this low prothrombin concentration per se is not significant since we have observed values below 5 per cent of normal without hemorrhagic diathesis. This view is born out by a study of 700 infants delivered by cesarean section, of which only one child developed hemorrhagic disease and it had experienced a labor of over sixty hours before delivery was effected. Under ordinary circumstances, at least five infants would have developed the disease.

It is our belief at present that there is no need for the administration of vitamin K during pregnancy beyond that present in the diet, unless there is specific clinical or laboratory evidence of deficiency or of liver and gallbladder disease, accompanied and associated with a reduction in the maternal prothrombin levels. If the infant is in need of this vitamin, and the evidence indicates that there is a further reduction in the prothrombin concentration in the first days of life, it can be given to the child parenterally after birth as a prophylactic measure. If hemorrhagic disease develops, the injections should be supplemented by transfusions.

Vitamin B_1.—Of the nine components of the vitamin B complex, vitamin B_1 is important with regards to pregnancy, since a deficiency causes symptoms of neuritis. Vitamin B_1 is excreted in the urine, which is readily understood because of its solubility in water. Harris and Leong find that about 8 per cent escapes in this way. Farley has devised a blood serum test for B_1 deficiency and with Horowitz used it in a study of 100 pregnant women. Low values were found in thirteen patients; of these seven had vomiting in early pregnancy, and ten developed neuritic symptoms. B_1 deficiency has been observed by Neuweiler in sixteen per cent of his cases during pregnancy.

Cowgill has shown that vitamin B_1 requirement is directly proportional to the *weight, caloric intake* and *basal metabolism*. Using his formula, Elsom demonstrated that pregnant patients gained sufficient weight by the 245th day of gestation to have a deficiency in vitamin B complex. This was substantiated clinically by evidence of neuritis, changes in the tongue and macrocytosis of the blood. Therapy, consisting of brewer's yeast or liver, caused an improvement in eight patients. Not infrequently, patients achieve the average normal weight increase of 24 per cent on the 200th day, wherefrom it can be postulated that a subclinical deficiency may be present earlier in pregnancy in these patients because of the increased weight and the demands of the fetus, since vitamin B_1 is not stored in large amounts in the body. This is particularly true when the increased basal metabolic rate in pregnancy of +16 per cent is taken into account. In experimental hyperthyroidism, Himmech, Goldfarb and Cowgill have proved an increased need for vitamin B_1.

Synthetic vitamin B_1, or *thiamin chloride*, has been successfully used in conjunction with calcium in the treatment of the *cramps* and *pains in the legs* of the pregnant patient. *Anorexia* also is said to respond readily to thiamin chloride, as does *vomiting* of early pregnancy. Under such circumstances impaired nutrition would continue and it is conceivable that a deficiency in more than one vitamin would result.

The hydremia, edema and increased cardiac output of normal pregnancy have a counterpart in beri-beri, for this disease is associated with edema, serous effusion and an enlarged heart. After the administration of vitamin B_1 to the patient suffering from beri-beri, marked diuresis occurs. Is hydremia of pregnancy an analogous condition? Hydremia produced experimentally in dogs by Cowgill, Rosenberg and Rogoff was associated with B_1 deficiency. Strauss does not think the edema in the toxemias of pregnancy is due to deficiency of B_1, since its administration produced no improvement. One case of eclampsia in Horowitz and Farley's study had no vitamin B_1 deficiency. Further studies in pregnancy are awaited with interest.

The vitamin B deficient child may develop a hypoglycemia, according to Sure, which fact may be of value in the management of the child born to a diabetic mother.

Jolliffe has pointed out that the national consumption of vitamin B_1 has been reduced by two thirds of that consumed in 1840, and that this marked decrease has been largely due to the use of extremely refined flour. This deficiency is of extreme importance since storage of B_1 is almost nil, making an adequate daily intake essential.

Vitamin B_2.—Vitamin B_2 (G or *riboflavin*) may have a relationship to pregnancy since the occasional patient complains of a sore mouth, may have a geographical tongue, and may develop dermatitis particularly about the vulva. There may be a tendency to a macrocytic anemia as observed by Elsom. The role of vitamin B_2 in hematopoiesis in pregnancy requires further study. We have used the B complex in the form of *brewer's yeast* in a large number of pregnant patients and have observed an improvement in the blood picture, partly because of the increase in the appetite that followed. In the treatment of the hypochromic anemias in conjunction with

iron, yeast has proved beneficial when the weight remained stationary.

Vitamin C.—The vitamin C requirement in the nonpregnant individual has been estimated at 50 mg. for a 60-kg. person. In pregnancy, according to Widenbauer, the need for C doubles itself. Gaehtgens places the safe level as 100 mg. daily, which is contained in 200 cc. of orange juice.

In a study of mothers on an adequate diet during pregnancy, Abt found that the vitamin C content of the mother's blood and the cord blood of the infants at delivery was identical, ranging from 0.66 to 1.4 mg. of ascorbic acid per 100 cc. of blood. He concluded that there was a complete diffusion of vitamin C through the placenta. However when an inadequate amount of vitamin C is available during gestation, Braestrup found that the maternal stores were depleted in order to supply the infant. Under such circumstances, he found that the mother's blood contained only 0.26 mg., while their infants had 1.07 mg. per 100 cc.

The normal range for vitamin C in the blood is from 0.3 to 1.8 mg. per 100 cc. This range should be regarded as an index of saturation, since readings of zero can be obtained without scorbutic manifestations. The normal level may be maintained with fruit juices and vegetables in the diet. Bleeding from the nose, gums and skin (petechiae), associated with a positive capillary fragility test may be regarded as clinical evidence of deficiency.

When heavy metals are used in the treatment of disease, Farmer has observed a decrease in the blood level of vitamin C. From this evidence, it may be advisable to administer C to pregnant women who are receiving antiluetic therapy.

Vitamin D.—Vitamin D is derived from animal sources and is abundant in milk and dairy products, fish oils and egg yolk, and is derived from the sterols. It is relatively scarce in the vegetables. The several available forms are *cod liver oil, ergosterol, viosterol,* activated *7-hydrocholesterol,* and *calciferol,* or pure vitamin D. It is of interest that ergosterol is derived from ergot, a drug of obstetrical significance.

The chemical formula for vitamin D is known, but the fact that urine and blood tests are not available has hampered accurate studies of requirements in pregnancy. However, an

estimation of the calcium-phosphorus relationship has been an index of sufficiency, since the metabolism of these substances is associated with vitamin D. This has been proved in the successful treatment of osteomalacia in pregnancy with vitamin D. In animals an excess of D has produced increased calcification of the blood vessels, kidney and trachea. However, the amounts needed for such a result is far in excess of even a large dose of vitamin D.

The optimum dose of vitamin D for adults is not known, and therefore the need during pregnancy is not definite. However, its importance to the infant is pretty well established, since when vitamin D is administered most of the evidence points to an improvement in the calcium reserves of the infant and therefore prevention of rickets. In tetany of the newborn, Maslow found evidence of calcium deficiency in both the mother and child. Toverud showed that pregnant dogs placed on a diet lacking in mineral and fat-soluble vitamins had puppies that developed rickets three weeks after delivery when placed on a deficient diet; whereas, if an adequate diet had been given during pregnancy, it took thirteen weeks before the puppies developed rickets on a deficient diet.

The daily requirement of vitamin D in pregnancy has been placed by Finola at 7000 units, together with 1.5 gm. of dicalcium phosphate. Such a regimen also prevents dental caries in the parturient woman, according to Drain, Plass and Obernst. The calcium is stored in the fetus from the fourth month, and an adequate intake will produce an increase in the density of the child's bones as well as a decrease in the size of the fontanelles at birth, while if inadequate amounts are available the converse holds true, according to Finola.

Vitamin A.—Vitamin A is derived from sources closely allied with D. *Carotene* has a marked A activity and is found in plants and vegetables, from which the cow derives most of its vitamin A. Milk and dairy products are rich in this vitamin. Fat-soluble vitamin A is stored chiefly in the livers of most species, and of course the livers of fish are a rich source.

The requirements of vitamin A have been estimated by Booker as 1400 to 2000 units, which is sufficient to prevent night blindness. In pregnancy the amount is probably greater, since Edmund and Clemesen found subnormal visual adapta-

tion in 50 per cent of the pregnant women admitted to the Copenhagen municipal hospital. It seems probably from this evidence that up to 5000 units may be required during pregnancy. This view is more tenable when we consider Ellison's findings that the livers of the newborn infants contain only 14 to 17 units per gram, whereas adults have 220 units per gram. This low concentration of vitamin A in the newborn has been studied from another angle by Straumfjord. He regards a large amount of vernix caseosa as evidence of vitamin A deficiency, and not a normal product of sebaceous glands, since vernix is to be found on the hands as well as the feet of the newborn. He treated twenty-five patients with large amounts of vitamin A and twenty-one infants had little or no vernix at birth, while of thirty-one untreated cases twenty-three infants had large amounts of vernix.

An adequate amount of bile is necessary for the absorption of carotene and to some extent vitamins A and K. The assimilation of fat-soluble vitamins, especially A and carotene, may be hindered by the presence of liquid petrolatum and mineral oil, according to Rowntree, Jackson and others. This finding is of great importance in pregnancy because of the frequent use of oil in the treatment of constipation.

Avitaminosis A causes atrophy and hyperkeratinization of the squamous epithelium anywhere in the body, and especially in the vagina, bladder and ureters. Mason has used this information in treating *senile vaginitis* successfully in thirty women, using cod liver oil. Sherman and Todhunter found abnormal estrus and an increased number of cornified cells in the vaginal smear of rats suffering from avitaminosis A. The vaginal smear technic has been recommended by Baumann for the detection of vitamin A deficiency. Susceptibility to infection is thought to be more prevalent when the stores of vitamin A are depleted. This may have a bearing on the development of *cystitis* and *pyelo-ureteritis* during pregnancy.

Hypervitaminosis A in the form of carotene causes a yellow skin which is transient and disappears in a few days following withdrawal of the dietary cause.

PUERPERAL AND NEONATAL REQUIREMENTS OF THE MOTHER AND THE NURSING CHILD

In the first days postpartum, considerable vitamin losses take place because of the changes in the maternal organism which characterize this period. Polyuria immediately postpartum results in the loss of several liters of fluid containing water-soluble vitamins. The involuting uterus causes further depletion of the vitamin stores, especially C. Puerperal infection, postpartum pyelitis, anorexia and other postpartum complications may necessitate supplementary vitamin therapy. Finally, the establishment of lactation creates a need for vitamins which is approximately equal to the amounts necessary during pregnancy.

In the antenatal period, certain vitamins such as C, E, K and B_1 passed the placental barrier, whereas only small amounts of A and D actually reached the child. During the establishment of extra-uterine life, there is a rapid depletion of the fetal vitamin stores. Nature recognizes this immediate need by providing a colostrum rich in vitamins. When lactation has been established, the titer of the milk of a mother on an adequate diet, without obstetrical complications, is usually sufficient for the infant. If it is not, or if the puerperium is abnormal, the maternal intake can be increased by additional vitamins which will be secreted in the milk; and finally, if this is not enough, or if lactation is unsatisfactory, the vitamins can be given directly to the nursing or bottle-fed infant. Pediatricians recognize and make practical use of this knowledge. The artificially fed infant may have a better controlled dietary than has the breast-fed child as far as vitamins are concerned. This is particularly true with regard to premature infants whose need for vitamins is perhaps twice as great as the full-term infant.

Vitamin E.—The need for vitamin E in lactation is not definite. This vitamin is present in newborn mice, as has been shown by Evans, who fed their tissues to deficient mice with a cure of the avitaminosis. A muscular paralysis has been described by Evans in suckling rats when the mothers were on a vitamin E deficient diet, and this finding has been confirmed by Morelle.

Vitamin K.—The vitamin K requirements for lactation

are unknown, and it is interesting to speculate as to its secretion in breast milk, particularly since this would give the infant an available supply. However, once the intestinal tract contains bacteria, the child may synthesize vitamin K, according to Quick.

Vitamin B_1.—The amount of vitamin B_1 in breast milk has been shown by Sure to be dependent upon the amount ingested by the mother. Since the storage of this vitamin is next to nothing, adequate intake is imperative, more so than during pregnancy, for Neuweiler found that 62 per cent of lactating women were deficient, whereas only 16 per cent were deficient during pregnancy. The daily requirements of B_1 for lactation has been placed at 1 mg. of thiamin chloride, by the League of Nations Health Committee. We are inclined to believe that at least twice this amount is necessary because of Neuweiler's statistics. The exact amount required by the infant is as yet indefinite, but sufficient amounts are necessary for growth and the prevention of infantile beri-beri.

Vitamin C.—The vitamin C requirement for lactation has been placed at 50 mg. by Baumann and Rappolt. If a sufficient amount is not available during gestation, the maternal stores will be depleted according to Braestrup, in order to supply the infant. However, in lactation, the converse of the situation occurs according to Gaehtgens and Werner; the maternal stores of vitamin C are conserved and the breast milk becomes deficient at the expense of the child.

The daily amount of vitamin C necessary for the average sized infant has been placed at 20 mg. This can be supplied by breast milk which contains 4 to 8 mg. per 100 cc., provided the mother is not deficient, and if she is, *cevitamic acid* will restore the milk to a normal level. The content of human milk is four times greater than raw cow's milk, and eight times greater (Daniel) than pasteurized milk. The infant has immediate need for vitamin C, for during the first ten days of life Braestrup has found that the amount in the blood decreases from 1.07 to 0.27 mg. It is during this period that the prothrombin concentration also decreases, and both of these factors may be responsible for the development of hemorrhagic disease of the newborn. Since the decrease is progressive, and begins early, Ingalls is of the opinion that infants

should receive supplementary vitamin C in the first week of life. There is no direct evidence that the infant can synthesize vitamin C, although Ray states that the chick can. Adequate levels can be maintained in the child by breast feeding, as shown by Mindlin, who demonstrated a concentration of 1 mg. in the blood of breast-fed infants on the fourteenth day, as contrasted with only 0.3 mg. in artificially fed infants. The healing of episiotomy wounds may be impaired by avitaminosis C. This statement is based on impaired wound healing observed in scorbutic children. However, Crandon in a carefully controlled study on himself reduced his vitamin C level to 0, maintained it so for forty-five days without sign of scurvy, and inflicted an operative wound which clinically healed normally.

Vitamin D.—Vitamin D is excreted in the milk, according to Light, and to insure an adequately supply the mother should receive about 800 units a day. This will provide the necessary 300 units required by the full-term infant to prevent rickets and assures adequate amounts for dentition and growth. The premature child needs almost twice as much. In general, breast milk contains more vitamin D than does cow's milk.

Vitamin D does not decrease the need for adequate *calcium* in the diet, since the drain on the calcium stores during lactation is greater than during gestation. About 2 gm. of calcium (1½ quarts of milk) are necessary daily, according to Macy and co-workers. This is especially true when pregnancies occur in rapid succession, for Garry has shown that multiparas require more calcium than do primiparas. The prevention of osteomalacia in lactation is dependent upon adequate calcium and D.

Vitamin A.—Vitamin A is very important to the newly born child, since at birth the liver contains about one-twentieth of the amount per gram found in the adult liver, according to Ellison. This need must be met by lactation and, to provide it, the mother must receive about 5000 units a day. Ordinarily, human colostrum is exceedingly rich in vitamin A, as is that of the cow, so that both the calf and the infant are provided with an available source, if the maternal breasts are lactating.

Vitamins L_1 and L_2.—Nakahara and co-workers are e
gaged in a study of the lactation vitamins L_1 and L_2 found
brewer's yeast, but the evidence is still in the rat stage.

SUMMARY AND CONCLUSIONS

Conception probably does not occur if avitaminosis
exists, since irreparable sterility results in the male, while th
female develops infertility, which may be improved by ade
quate dosage of vitamin E. As far as habitual abortion i
concerned, the Council on Pharmacy and Chemistry of th
American Medical Association has recently concluded that n
claims can be made for vitamin E. The value of vitamin E
in the prevention of abortion is also far from conclusive
Until further evidence has accumulated, raising the hopes o
prospective parents is undesirable.

There is reasonable doubt that a healthy woman on a sup-
posedly adequate diet receives sufficient vitamins to fulfill the
requirements of pregnancy because of faulty preparations of
foods and dietary aberrations. The use of mineral oil and
liquid petrolatum to combat constipation during pregnancy
may also hinder assimilation of the fat-soluble vitamins, espe-
cially A.

The increased vitamin requirement during pregnancy is
due to certain physiologic changes, including the average in-
crease in weight of 24 per cent, the elevated basal metabolic
rate of 16 per cent and the hydremia and physical anemia—
not to mention the needs of the growing protoplasmic mass
of the fetus. Data have been presented which indicate that
from 6 to 50 per cent of normal pregnant woman show labora-
tory evidence of deficiency with regard to one or another of
the vitamins. We are beginning to realize that a deficiency
in one vitamin may be interpreted as a deficiency in other
vitamins, so that a clear-cut clinical picture of a single de-
ficiency is not often obtainable. It must be obvious even to
the skeptic that the maternal stores of vitamins are reduced
in pregnancy, while specifically vitamin B_1 is not stored at all.
Subclinical depletion, with or without clinical symptoms, is
more amenable to treatment than are the pathologic manifes-
tations of true deficiency. The increased requirement in preg-
nancy must be met by either adjusting the diet or by supple-

mentary administration of commercial preparations, especially when clinical symptoms or laboratory tests corroborate the diagnosis.

When complications of pregnancy are present, such as nausea, vomiting, toxemia, hyperthyroidism, diabetes, tuberculosis, anemia and infections, supplementary vitamin therapy, beyond correction of subclinical deficiency or to meet the increased requirements of pregnancy, is necessary.

In general, the placenta is not a barrier to the passage of vitamins C, E, K and B_1, whereas only small amounts of A and D reach the child. However, in the first days of life there is a progressive decrease in the vitamin stores of the infant, especially vitamins C and K. The liver of the infant is also very deficient in vitamin A. The hypoprothrombinemia of the newborn is probably due to liver insufficiency and associated avitaminosis K. *There is no more need for the antepartum administration of K during pregnancy to prevent hemorrhagic diseases of the newborn, than there is for C to prevent infantile scurvy, or D to prevent rickets, or B_1 to prevent beri-beri;* except *when clinical observations and laboratory tests have disclosed a maternal vitamin deficiency.* To give vitamins to the mother during pregnancy or labor in the hope of treating the infant is rather uncertain, since if the maternal stores are deficient, little of the vitamin will be available for passage through the placental barrier. If vitamins are given during labor, the patient may deliver before much has reached the infant. It is more logical to give vitamins A, C, K and D *directly to the child at the time of delivery,* by the parenteral route if it is considered necessary, thereby controlling exactly the amount administered. Parenteral administration of certain vitamins to the child at birth may become a routine procedure, just as silver nitrate is now instilled into the eyes of every newborn child.

In the puerperium, as during gestation, infections such as pyelitis, puerperal infection, breast abscess and respiratory disease may require an increase in the vitamin intake since the appetite may be impaired, in which event a high vitamin diet will prove of no benefit. Finally, the onset of lactation creates an added requirement, which is generally the same for each vitamin as during pregnancy, in order to maintain an adequate

supply for the mother. Such a regimen will provide colostrum and milk rich in vitamins, so that the progressively decreasing stores of the infant during the first days of life may be replenished. Again, an adequate diet may be sufficient, but if there is doubt, or when puerperal complications exist, supplementary vitamin therapy is to be recommended. In the event that the mother does not lactate, or the infant must be artificially fed, the required vitamins should be given orally or parenterally to the child, beginning as early as the first day of life.

NOTE.—The Warner, Brinkhous and Smith technic was used for the prothrombin determinations which were made possible through the kindness of Dr. William DeWitt Andrus under a grant from the John and Mary R. Markle Foundation. The technical assistance of Miss Cesira Macri and Miss Marion Ranges is gratefully acknowledged.

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THE MANAGEMENT OF PUERPERAL SEPSIS

THE treatment of puerperal infections must be considered from two aspects, that of *prevention* and that of *therapy* of the sick patient.

PROPHYLACTIC MEASURES

Exogenous Infections.—The present conception that such infections can be caused by two groups of organisms, the exogenous and the endogenous, has a definite bearing on the question of prevention. Bacteriologic studies in regard to the source and method of transmission of infections caused by certain types of organisms in the exogenous group have led to the formation of certain principles designed to block the occurrence of such infections.

Among the organisms responsible for the exogenous type of infection are the *beta hemolytic streptococcus*—usually Group A; the *staphylococcus*, the *colon bacillus*, the *pneumococcus*, the *gas bacillus*, the *typhoid bacillus* and other rarer organisms. Certain of these organisms, most commonly the beta hemolytic streptococcus and more rarely the pneumococcus, have their source almost always in the nasopharynx of patient or attendant or in a septic focus somewhere in the vicinity of the patient. Most of the other organisms have their source in the intestinal tract. The problem of prevention depends on blocking of the transmission of these organisms from their respective sources. Since the sources of such infections are varied, the method of prevention must also differ.

Beta Hemolytic Streptococcus Infections.—It has been conclusively shown that the common sources of the Group A

beta streptococci are the nasopharynx of the patient or h attendants, or from some septic focus in the vicinity of t patient. These organisms are not found normally in t vagina. Transmission to the genital tract may take place b direct inoculation of the fingers of the attendant or patien by droplet inoculation of fingers of patient or fingers of a tendants or of the external genitalia; or by transfer by mear of air and dust from a septic focus. These facts, long su pected and now definitely proved, lend a solid basis to th measures employed to prevent infections caused by the Grou A beta hemolytic streptococcus. Similar measures shoul prevent primary pneumococcal infections.

The principal measures employed to prevent such infe tions on the Obstetrical Service at Bellevue Hospital are a follows:

1. Antepartum patients admitted to the Obstetrical Servic with febrile complications (other than pyelitis) are placed i a small observation ward. Immediate steps are taken to de termine the cause of their fever. If it is due to an infectio caused by the hemolytic streptococcus, such patients are trans ferred to the medical service.

2. Patients admitted with intrapartum fever are delivere in a special delivery room and are transferred to the isolatio ward immediately after delivery. Cultures are taken imme diately to determine the infecting organism.

3. Cultures are taken immediately on all patients who hav a temperature of 100° F. or more in the postpartum period Such cultures are read grossly in sixteen hours and if evi dences of hemolytic streptococci are present, the patient i transferred immediately to the isolation ward. If hemolytic streptococci are not found, the patient may be kept on the obstetrical service under close observation for a few days. Should fever continue, the patient is put in isolation.

The above measures are aimed at eliminating patients from the obstetrical service who may act as sources of infection.

4. Doctors and nurses caring for patients during labor, de- livery and the postpartum period are required to mask both nose and mouth.

5. Vaginal examinations are carried out with the same careful preparation of the patient and examiner as is used in

the actual delivery of the patient. Strict precautions against direct or indirect vulval contamination are employed in rectal examinations.

6. Nurses and doctors suffering from acute upper respiratory infections or from evidence of subacute or chronic nasopharyngeal foci are excluded from the active care of patients until such infections have cleared up or until negative cultures for hemolytic streptococci have been obtained.

7. Patients are warned against touching the vulva during labor.

The latter measures are designed to prevent transmission of hemolytic streptococci from carriers.

A word might be said here as to *normal carriers* of the hemolytic streptococcus. For a number of years cultures have been taken from the nose and throat of individuals working on the obstetrical service. Such cultures have been obtained from doctors, interns, students and nurses. Positive cultures are usually found in under 1 per cent of these individuals in summer and fall. By February such cultures are often positive in 10 per cent of instances and by late spring have again dropped to about 1 per cent. In the winter of 1934, when we had our last serious group of infections by the hemolytic streptococcus, the incidence of carriers on the staff rose to 25 per cent. Obviously, the elimination of such carriers until negative cultures have been obtained would cripple the personnel of the service. We have depended on the use of masks to prevent transmission of these organisms. Only attendants suffering from acute infections or with obvious foci have been prohibited from attending patients. The occurrence of severe hemolytic streptococcus infections on both the obstetrical and gynecological services have been limited to the portion of the year between late November and early May, a period related exactly to that of the increased frequency of normal carriers.

Again, comment may be allowed as to the *efficiency* of the above-mentioned measures. Since October, 1933, routine lochial cultures have been taken on the obstetrical service at Bellevue Hospital from patients with postpartum fever or with suspected infections. Of 11,400 patients delivered during this time, 1180 were morbid on a standard based on a fever of 100.4° F. Only 69 of these cultures showed hemolytic

streptococci—an incidence of 2.7 per cent. In only 35 of these cultures were hemolytic streptococci the predominating organism. On the gynecological service 622 cervical cultures were taken from patients suffering from incomplete abortion complicated by fever. Eighteen of these cultures, or 2.9 per cent, showed hemolytic streptococci. These organisms were not classified by serologic methods. Many of these patients showed no clinical evidence of the presence of a virulent organism, having no fever of even short duration. We feel justified in assuming that the incidence of Group A infections must fall well below 1 per cent on both services.

On the basis of comparison of the results obtained from cultures taken on the two services, one cannot argue that the methods of prevention used on the obstetrical service are the sole reason for the low incidence of these infections. Such infections have been rare during the past few years all over New York City. In an epidemic year we may find that our preventure measures are not completely effective. However, the enforcement of such measures are of great value in making all attendants aware of the constant danger of transmitting infection to patients.

Colon and Gas Bacillus Infections.—The most important organisms remaining for consideration in the exogenous group include the colon bacillus and the gas bacillus. The colon bacillus is transmitted to the genital tract (1) by a complicating infection of the urinary tract, or (2) by fecal contamination of the genital tract during labor and delivery. The first source can be eliminated in many instances by the early treatment of such urinary infections. Sulfanilamide and related drugs have proved most useful in this control. The prevention of fecal contamination depends on the maintenance of an empty rectum during labor and a careful technic during delivery. These latter precautions are equally important in the prevention of gas bacillus infections.

Endogenous Infections.—While the principles of prevention in exogenous infections are quite definite, it is much more difficult to devise methods of prevention of endogenous infections.

Anaerobic Streptococcus Infections.—The principal organism which can be definitely associated with this type of in-

fection is the anaerobic streptococcus. This organism is present in the vaginal tract of a large percentage of normal women before delivery. It is said that this is the only site where it may be found with any frequency. In most instances it gives no evidence of pathogenicity in the postpartum period. Infections with this organism follow most often a prolonged exhausting labor, often with ruptured membranes, and usually terminated by difficult operative procedures. Two possible courses of prevention suggest themselves. Careful antepartum study should anticipate a certain proportion of such labors and should lead to the decision to deliver such patients by *cesarean section* rather than by the vaginal route. It should be remembered, however, that such labors do not merely result from defects of the bony pelvis but also from variations in the soft parts, deficient maternal forces and malposition of the fetus. Such a measure of prevention is easier to outline in theory than to put into practice. Early decision during labor as to the method of delivery and the choice of the proper type of cesarean section will minimize the danger of operation. Recently devised methods of roentgen pelvimetry, especially when utilized during labor, are a great aid to clinical judgment in arriving at this decision.

Another method of prevention of endogenous infections consists in the attempt to sterilize the vaginal tract during labor by means of *antiseptic agents*. The efficacy of such measures is a controversial point. Brown reports excellent results in patients treated with vaginal instillation of acriflavine and glycerin during labor. We have had no experience with such measures at Bellevue Hospital but propose to give Brown's method a thorough trial during the coming year. This group of infections presents a host of unsolved problems to the investigator. Until some of them are solved, these infections cannot be controlled.

The prophylactic use of *sulfanilamide* in patients at term has been suggested and there is experimental evidence to show that it might be of value. The infrequency with which Group A beta streptococcus infections are encountered in this vicinity leads to the conclusion that this measure would not be practical under present circumstances. The prophylactic use of this drug under epidemic conditions or in individuals who have

been exposed to such infection when close to term is another matter. Here such therapy may prove of great value.

TREATMENT

Let us turn now to the treatment of puerperal infections once they have established themselves. Such treatment can be considered under two heads, *surgical* and *medical.*

Surgical Therapy.—Surgical therapy involves relatively few procedures, the most important of which are hysterectomy, ligation of veins draining the uterus, drainage of peritonitis, drainage of parametrial abscesses, and the removal of retained secundines from the uterus. The inadequacy of some of these procedures as shown at the autopsy table, together with the marked tendency of the individual to localize infection spontaneously and to recover, has led to the abandonment of some of these procedures.

Hysterectomy is rarely performed in these cases, and in the records of Bellevue Hospital for the past seven years only one such operation has been done for this indication. The patient had a degenerating fibroid, infected with Staphylococcus aureus. She had a high remittent fever. The blood culture was negative. Recovery promptly took place after the removal of the uterus. After a trial, *ligation of thrombosed veins* has been abandoned because of the uncertainty as to the exact system of veins involved, and of the dubious results following such operations. Most authorities advise against the *drainage of general peritonitis* arising from a uterine focus. Our own experience at Bellevue leads us to believe that this operation tends to hasten the fatal termination. Surgical intervention at present is limited to the *drainage of localized peritoneal exudates* and *paremetrial abscesses.* The latter procedure is particularly effective and usually leads to rapid recovery.

Finally one may mention the *surgical removal of retained placental fragments.* Such fragments are present far oftener after early abortion than after full term delivery and the factor of infection frequently complicates their presence. Many authorities urge extreme conservatism until all clinical evidence of infection has been for some time absent before resorting to surgical removal. On the other hand, the surgical removal

of these fragments from the patients showing clinical evidence of infection with organisms of low pathogenicity is followed by rapid recovery in most instances. When such cases are infected with Group A beta streptococcus, chemotherapy should be used preliminary to operative removal of the placental remnant.

Medical Therapy.—*General Care of the Patient.*—The main features of general care of these patients consist in *bed rest, fresh air, sunlight, ample diet,* and expert *nursing* attention. The gastro-intestinal disturbances secondary to a spreading pelvic infection may make necessary suction drainage of the stomach and intestinal tract and the use of parenteral *fluids* containing glucose and electrolytes. The marked anemia frequently observed in these infections must be combated with repeated *transfusions.* Less effort is expended in the elimination of pelvic exudates since it has come to be realized that processes of both parametritis and thrombophlebitis represent important defensive mechanisms which tend to limit the spread of organisms. Once the spread is limited and the full defense of the patient is mobilized, such exudates tend to disappear spontaneously, provided abscess formation does not take place. Patients seen a year after recovery from the most severe pyogenic puerperal infection rarely show on examination any evidence of any residual lesion.

Chemotherapy.—In addition to the general care of the patient, many special forms of therapy have been employed in these infections. Vaccines, serums, and a host of drugs have been used only to be discarded as valueless. The advent of sulfanilamide and its related compounds is, therefore, a great advance.

However, it must be pointed out that these drugs are of value only in certain types of infection which, at present, constitute but a small percentage of the total number occurring in this neighborhood. To use them rationally an early diagnosis must be made as to the nature of the invading organism. This can be done only on the basis of a positive blood culture or on the finding of a predominant organism in the lochial or uterine culture. In the majority of instances, blood cultures are sterile and lochial and uterine cultures show a mixed group of organisms. The most frequent bacteremia observed on

these patients at Bellevue Hospital is that caused by the anaerobic streptococcus; the second most frequent, that caused by the beta hemolytic streptococcus. Colebrook reverses this frequency in his reports, which deal of course with much larger groups of cases. Bacteremias caused primarily by pneumococcus, by staphylococcus, by colon bacillus and by gas bacillus infections are rare. Beta hemolytic streptococcus infection is the commonest clear-cut infection to be detected by means of lochial or uterine cultures. As has been noted, it is rarely found at the present time. Gonorrheal infections are usually disclosed by the examination of direct smears from the cervix and urethra. Cultural methods are available and are more efficient, but they have not yet proved suitable for use as a routine diagnostic measure.

It can be stated, from the clinical and laboratory experience of the past few years, that chemotherapy is of great value in puerperal infections caused by the beta hemolytic streptococcus, pneumococcus, staphylococcus and gonococcus. Such treatment has proved of no value in genital infections caused by the anaerobic streptococcus and colon bacillus. Doubt has recently been expressed as to the value of chemotherapy in gas bacillus infections.

The most important group of infections affected by these drugs is that caused by the *beta hemolytic streptococcus*. One can classify patients showing this infecting organisms into four groups: (*a*) patients with positive cultures and no evidence of disease; (*b*) those showing positive cultures and slight degrees of fever; (*c*) those showing positive cultures, high fever, but no evidence of spread past the uterus; and (*d*) those showing positive cultures, high fever, bacteremia and other evidences of spread past the uterus. The last two types of cases can be called *severe local* and *severe spreading infections*. Chemotherapy should be limited to these two groups. Colebrook reports a mortality of 22.8 per cent in patients with this degree of infection from 1930 to 1935. Since the advent of sulfanilamide this mortality has been reduced to 5.5 per cent. There are no reports in this country that can be compared to his since no one observer has treated such numbers of this infection.

Some idea of the infrequency with which severe infections

with this organism are encountered at present may be gathered from the fact that, in spite of careful search, one year elapsed before finding a severe hemolytic streptococcus puerperal infection at Bellevue Hospital to treat with sulfanilamide. Since this time we have seen eight patients with postpartum or postabortal sepsis with bacteremia caused by this organism, all of whom have been treated with sulfanilamide. Five recovered and three died, a mortality of 37.4 per cent. Between January 1, 1933, and September 1, 1936, twelve such patients were admitted. Ten of these died, the mortality for the group being 83.3 per cent. While this is a small series, nevertheless it shows a marked improvement in our results. Furthermore, all the patients with severe local infections have recovered and none has developed bacteremia after treatment was begun. It is of interest that two of the patients who died showed suppurative thrombophlebitis of the pelvic veins and one, bacterial endocarditis. Lockwood has pointed out that this type of lesion, among others, is not favorably affected by chemotherapy. Sulfanilamide, in our hands, has proved the most satisfactory drug for this type of infection. It can be used over long periods with relatively little disturbance of the patient. Some idea of the details of this treatment can be gained by a short review of one of these cases.

Mrs. K, aged twenty-seven, was admitted to the hospital on January 29, 1940. She had introduced a catheter into the uterus on January 27 and this was followed by slight bleeding and on the next day by chills and fever. On examination she was found to be about two and one-half months pregnant, moderate bleeding taking place through a patulous cervix. No parametritis was present. Her temperature was 104.8° F. On January 30 her blood culture and cervical culture were reported as positive for hemolytic streptococci. She was immediately put on sulfanilamide, a total of 18 gm. being given in the next forty-eight hours. Three pituitrin series were given in a vain effort to empty the uterus. On February 1 her temperature was 100° F. The uterus was emptied by curettage. The preoperative blood culture was sterile, but the cervical culture still showed hemolytic streptococci. No reaction followed the curettage.

During the first forty-eight hours postoperative the dose of sulfanilamide was diminished to 6 gm. a day. During the next seventy-two hours, it was dropped to 4 gm. a day. The patient's temperature fell to normal and on February 5 the cervical culture was reported as sterile. Therefore treatment was discontinued. She developed four abscesses at the site of the pituitrin injections. These all were incised and drained. Hemolytic streptococci were recovered from each. Healing took place uneventfully and the patient was discharged on February 14, showing no evidence of her severe infection.

A few brief remarks may be made on the other types of infection suitable for chemotherapy. *Gonococcal infections* respond readily in the majority of instances to sulfanilamide. In refractory cases, additional treatment with *sulfapyridine* will often clear up this infection. The value of sulfapyridine, both with and without serum, in *pneumococcal infections* has been abundantly demonstrated, and this drug should be of benefit in both primary and secondary genital infections. We have had no experience in its use in primary infections. *Sulfathiazole* and *sulfamethylthiazole* appear to be better agents for use when *staphylococcal infections* are present. No opportunity for their use has presented itself at Bellevue, but I am acquainted with the details of one case of puerperal septicemia in which recovery took place under treatment with the latter drug.

One can say, then, that the advances in chemotherapy have been of great assistance to the obstetrician in the treatment of a small group of cases caused by certain specific organisms. Fortunately in this group we find infections of the most severe and fatal type, notably the Group A beta streptococcus infections. In the vast majority of puerperal infections a mixed group of organisms is present. In a few of these cases we know, and in a large number we have cause to suspect that the *anaerobic streptococcus* plays a leading part. There is no known agent which affects favorably infections caused by this organism. This may well be due to the type of lesion produced which is, in a high proportion of cases, suppurative thrombophlebitis. Perhaps some future discovery will produce a successful agent against this type of infection. At present we must rely entirely on prevention to diminish its incidence, severity and mortality.

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CLINIC OF DR. HARRIET C. McINTOSH

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ROENTGEN TREATMENT OF PUERPERAL MASTITIS

ALTHOUGH the use of irradiation in the treatment of acute and chronic inflammatory conditions is about as old as the discovery of *x*-rays, there is still great variation of practice in this country in the extent and enthusiasm with which it is employed. Among the conditions in which the treatment has received wide acceptance—excluding the strictly dermatologic field—may be named furuncles, carbuncles, erysipelas, postoperative parotitis and tuberculous adenitis. Curiously, little has appeared in the literature on irradiation of puerperal mastitis, and almost nothing in English. In February, 1939, Elward and Dodek[1] presented a paper on the subject, with a bibliography of twenty-two titles. In April, 1939, the author[2] reported forty-four cases before the Medical Society of the State of New York. Both papers were subsequently published in 1940. I will not repeat here a discussion of the literature, which is already available in the paper by Elward and Dodek.

The rationale of the effect of *x*-ray on inflammation in general has been widely studied and discussed, but is still incompletely understood. Numerous contributions on the topic have appeared, notably by Hodges,[3, 4, 5] Desjardins,[6] Carty,[7] and Pendergrass and Hodes.[8] There has been vigorous and prolonged argument as to whether small doses of *x*-ray stimulate or depress this or that component of the tissues. One theory of the effect of small doses of *x*-ray on inflammations is that the leukocytes, being especially sensitive, undergo alteration or destruction, liberating some ferment or antibody which helps to resolve the inflammatory process.

Pendergrass and Hodes consider that the effect of irradiation on the local vascular system is of greater importance, the principle being the transformation of what was originally an area of *passive hyperemia* into an area of *active hyperemia*. Their recent article gives the most extensive review available on the mechanisms involved in the irradiation of inflammations. They do not report specifically upon acute mastitis.

My material consists of 115 cases treated from October, 1938, to October, 1940, ninety of these from the Woman's Hospital and twenty-five from the New York Infirmary for Women and Children. Most if not all of the symptoms of redness, heat, swelling, induration, pain and fever were present in all cases of the group. Simple engorgement of the breasts, no matter how painful, was not treated by roentgen therapy. The series comprises sixty-eight primiparae and forty-seven multiparae. The oldest patient was thirty-nine years of age and the youngest eighteen. The average age, reported earlier in forty-four cases as 26.8 years, remained exactly the same in the present larger group of 115 cases. The right breast was involved in forty-seven cases, the left in forty-nine, and both in nineteen. Originally I had the impression that double breast involvement was more recalcitrant to treatment, but this has been subsequently disproved. The time of onset after delivery showed nothing of significance, except a predilection for the second week. A single case occurred two months before delivery and one as late as five months after.

ADVANTAGES OF x-RAY TREATMENT

As it is the experience of all practicing obstetricians that in a large proportion of cases acute puerperal mastitis subsides spontaneously or by the use of the usual palliative ice bags and supporting binders, a new form of treatment must justify itself by improved results in one or more of the following respects: (*a*) more prompt relief of symptoms; (*b*) more rapid resolution of the process; (*c*) reduction of the percentage of cases going on to suppuration. Promptness of relief of symptoms and rapidity of resolution are difficult to state in statistical terms in such a relatively benign condition, especially as one cannot prove that a given case might not have subsided as well without treatment. But the clinical impression that

these benefits ensue from x-ray treatment is so marked in both hospitals from which this material is taken that the cases are sent to the x-Ray Department routinely as soon as symptoms and signs are noted—house patients usually within twenty-four hours. I have had them as early as three hours after onset. In these very early cases it is no uncommon thing for a young woman to appear for her first treatment with a red, swollen, painful breast and a temperature of 103° to 104° F., miserably uncomfortable, and to return the next day, adorned with smiles and a bright hair ribbon, pain gone, redness fading, mass reduced by half, and her temperature at or near normal.

The following history is offered on an out-patient, mother of a five-month-old baby which she was nursing.

Case I.—Primipara, aged thirty-seven. The breast was sore on arising in the morning, and became rapidly more painful during the forenoon. On examination the outer hemisphere of the right breast was reddened and tender; the patient's temperature was 101° F. She was given a small dose of x-rays to a 12 by 10 cm. portal around noon. By supper time the temperature had fallen to 100° F. and the pain was diminished. At bedtime the temperature was 99° F.; the breast was sore but not painful. Examination on the second day showed induration two-thirds resolved, tenderness slight, no redness, pain or temperature elevation. Following a second treatment there was complete resolution with no recurrence.

SUPPURATION IN TREATED CASES

The question of suppuration must be considered from a baseline of untreated cases. The Woman's Hospital for the three years, 1936 to 1938, had 4568 deliveries. Following these 152 of the mothers had nonsuppurative puerperal mastitis, and thirty-five, or 0.7 per cent, had breast abscesses. This percentage of abscess corresponds closely to that of 0.55 per cent reported by Dippel and Johnston[9] in a study of 20,258 women from the obstetrical service of the Johns Hopkins Hospital between 1896 and 1934. On the basis of this close correspondence and the large numbers involved, our material can, I think, be considered typical of good hospital practice in this country. To recapitulate, then, the Woman's Hospital figures for the three years in question showed thirty-five breast abscesses in 4568 deliveries, or 0.7 per cent; 152 cases of nonsuppurative puerperal mastitis in 4568 deliveries, or 3.3 per

cent; 187 cases of puerperal mastitis altogether, of which 18.7 per cent went on to suppuration. The generally reported figure for suppuration is around 20 per cent.

Patients receiving *x*-ray numbered 115, but of these nineteen had bilateral involvement. In evaluating results of treatment it seems more satisfactory to count breasts rather than patients, particularly as in several cases one breast resolved and the other suppurated. There were, therefore, 134 breasts treated. Of these, 112 resolved and twenty-two, or 16 per cent, suppurated, either breaking down of themselves or requiring incision and drainage. This represents a slight improvement over the percentage of 18.7 in the group of the preceding three years which did not receive *x*-ray, but a change of less than 3 per cent might occur spontaneously over a period of several years. However, a breakdown of my own figures is exceedingly interesting, and casts light on what, in this condition, *x*-ray is good for (Tabulation).

TABULATION

SUPPURATION IN PUERPERAL MASTITIS

	Number of Cases	Treated by *x*-Ray	Nonsuppurative	Suppurated	Per Cent Suppuration
Woman's Hospital, 3 yrs., 1936–1938	187	0	152	35	18.7
Woman's Hospital and New York Infirmary, 1938–1940	134*	x	112	22	16
Treated first 24 hrs. after onset	75*	x	74	1	1.33
Treated 48 hrs. to 1 mo. after onset	59*	x	38	21	35

* Breasts, not cases.

Seventy-five breasts were treated within twenty-four hours of onset of mastitis, and of these one, or 1.33 per cent, suppurated. This was in one of my earliest cases. The patient had only one treatment, after which the suppuration regressed so much she was sent home with a small core of induration remaining which subsequently flared up. I now realize that she should have had a little more treatment.

Fifty-nine breasts were treated from forty-eight hours to

one month after onset of mastitis, and of these twenty-one, or 35 per cent, suppurated. It is, therefore, apparent that the later cases do not do as well. This is not to say that treatment should not be attempted, as resolution did take place in 65 per cent of them.

Analysis of Suppurating Cases.—In the sole early case of suppuration, noted above, more treatment should have been given.

In six cases the mass was partly fluctuant when seen. *x*-Ray was deliberately used to demarcate the process and hasten or increase the evacuation of pus.

One case showed a hard mass of a month's duration. *x*-Ray was used to soften and break down the process, which was accomplished in two treatments, with rapid healing.

Two cases with bilateral involvement showed resolution in one breast, suppuration in the other. In one, the right breast resolved in two treatments. The process in the left came up ten days later, producing a small area of central softening which evacuated spontaneously after three treatments.

A group of twelve cases represents primarily the class least likely to resolve under irradiation. All were first seen late, three days to three weeks after onset. They showed hard, tender masses, little or no redness, usually no temperature—a low grade, indolent process. *x*-Ray here served in all but two cases to hasten breaking down. In two, hot applications were also required, as well as a more prolonged waiting period.

A graphic and interesting example of the advantage of *x*-ray treatment is cited in the following case, with bilateral breast abscesses, in which one breast was treated surgically and the other by *x*-ray. This case has been spoken of before, but seems to merit repetition as illustrative of the factor of rapid healing with irradiation.

Case II.—Para II, aged twenty-eight. The patient had two successive abscesses in the left breast three and four weeks respectively after delivery, with incision and drainage but no *x*-ray. Seven weeks after delivery she presented herself at the clinic with a tender, reddened area in the right breast measuring 8 by 8 cm. The mass was hard for the most part, but had a fluctuant center. After three treatments of 50 roentgens each, the center opened spontaneously and considerable pus was evacuated. With two more treatments the surrounding infiltration and central abscess healed, while the two abscesses on the opposite side, four and three weeks older respectively, were still draining.

TECHNIC

As puerperal mastitis is a benign condition, the first requirement of treatment is that the *x*-ray dosage to skin, mammary apparatus and underlying lung should be harmless. Fortunately the most effective dosage is small, far below the limits of possible detriment. Some workers employ high voltage, but I prefer low voltage, in the range of 120 to 125 kilovolts, with aluminum filtration. Small individual doses are given, 50 to 60 roentgens at a time. Occasionally through a very small portal I give 75 roentgens. Treatments are usually given daily. The number of treatments required in this group of 134 breasts was as follows:

32	received	1 treatment each.
40	"	2 treatments.
29	"	3 "
15	"	4 "
18	"	5 or more treatments.

Three patients received seven, eight and nine treatments respectively, but with the following pattern: Three to five treatments were given to fields of diminishing size, with considerable but incomplete resolution. After a wait of a week or more, several more treatments were given on a small central core of induration.

To summarize, 101 breasts required one to three treatments; thirty-three breasts required four or more. At 50 roentgens per treatment, even the highest total stated, considering the spacing of the dose and the size of the portals, adds up to considerably less than an erythema dose. However, a word of caution should be given to those not experienced in this technic. Trained roentgenologists know, as most clinicians do not, that one of the most important quantitative factors in dosage is the size of the skin field exposed to irradiation. I have never given more than two or three treatments (of 50 or 60 roentgens) without reducing the size of the portal. A given lesion may require treatment through a skin field 12 by 15 cm. at the first visit, but by the third—if a third is necessary—the field may be reduced to 8 by 8 cm.; by the fourth to 5 by 5 cm. Such a scheme does not necessarily hold for other types of inflammation, in other parts of

the body, but I feel that if puerperal mastitis is going to respond to irradiation it will do so in at the most five treatments of the size described, almost without exception. The only cases in which I have given more are those few where a second cycle is given, through a greatly reduced field, after a waiting period, and I emphatically do not recommend this as a general practice. Irradiation improperly administered or unduly prolonged is of course dangerous.

SUMMARY

1. The advantages of roentgen treatment of puerperal mastitis are as follows: (1) Prompt relief of pain. (2) Shortened duration of the process. (3) Striking diminution in the number of cases going on to suppuration if treated within twenty-four hours of onset—1.33 per cent in this series against an average of 18 to 20 per cent in cases not receiving *x*-ray treatment. (4) If suppuration occurs, more prompt localization of the process and a shortened period of healing.

2. Least responsive to irradiation, or least likely to disappear without suppuration, are the late, subacute cases, with little or no temperature and few symptoms.

3. Technical recommendation: small doses of *x*-ray, of limited number, preferably of low voltage type.

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CLINIC OF DR. GEORGE LOVERIDGE BOWEN

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MANAGEMENT OF PLACENTA PRAEVIA

PLACENTA praevia is generally classified as: (1) *complete* placenta praevia, in which the internal os of the uterine cervix is entirely covered by the placenta; (2) *partial* placenta praevia, in which the internal os is partly covered by the placenta, and (3) *marginal* placenta praevia, in which the placenta approximates the internal os but does not encroach upon it.

Frequency.—In two large series of deliveries recently reviewed, placenta praevia occurred in a ratio of 1 to 105 in 26,116 labors,[1,1] and 1 to 134 in 34,879 labors.[4]

The relative frequency of the three types of placenta praevia is reported in several large hospital series as follows:

	Complete, Per Cent	Partial, Per Cent	Marginal, Per Cent
Bellevue Hospital, New York[1,2]	23	25	42 (10% unclassified)
Charity Hospital, New Orleans[4]	37	33	30
Chicago Lying-In[3]	34	13	52
Maryland University and Baltimore City Hospitals[5]	26	26	47

The variations in the frequency of the three grades may be due to the difference in the amount of dilatation at the time vaginal examinations are made, making accurate diagnosis difficult.

Etiology.—The etiology is unknown, although various theories have been advanced to explain the low implantation of the placenta. We do know that the condition occurs more frequently in multigravid than in primigravid women, and more frequently in white than in Negro women.

Symptoms.—The cardinal symptom is *painless bleeding.* This is usually seen in the last trimester of pregnancy, although it may occur in the earlier months. Reports show that 40 to 50

per cent of all women who experience this symptom in the last trimester have placenta praevia.

Diagnosis.—Even though the bleeding is slight the patient should be placed in a hospital for study and diagnosis. Transportation entails no great risk provided an internal examination is not done in the home. As the clotted blood provides good hemostasis it should not be dislodged, nor should any attempt be made to pack the vagina. Effective vaginal packing is difficult with ideal surroundings and equipment, and even when properly done it increases the risk of infection. It may be desirable to give the patient ¼ grain of morphine before she is moved.

Immediately following admission to the hospital the blood is typed and, if time permits, a complete blood count and hemoglobin and cell volume determinations are made.

After the initial hemorrhage, the patient with sedation and bed rest may not bleed again for intervals varying from a few hours to several days. Therefore, if the bleeding stops, the patient may be kept in bed for four or five days before any vaginal examination is done.

During this waiting period *roentgenography* may be helpful in making a diagnosis. Ude et al.[6] in 1934 reported filling the bladder with a radiopaque substance before taking *x*-ray pictures. This shows the relationship between the bladder and the lower uterine segment. When the placenta is implanted low on the anterior wall, its structure is interposed between the presenting part and the lower uterine segment and thereby decreases the proximity of the presenting part to the bladder. However, Carvalho[7] obtained some false positives where factors other than a low implanted placenta were present which caused an upward displacement of the fetal head. In addition, the procedure was found of little value when the placenta was implanted low on the posterior wall. Brown and Dippel[8] have reported accurate determination of placental location by *soft tissue* roentgenography after distending the bladder with air. Further work along these lines may develop more practical and helpful aids.

At present a *sterile vaginal examination* is our most satisfactory method of diagnosis. For this examination the patient must be taken to the delivery room, complete aseptic technic

is essential, and all equipment and personnel must be in readiness to institute any necessary procedure. In some clinics a team is scrubbed and the operating room is set up for a cesarean section before the vaginal examination is begun. The resulting decrease in maternal mortality, as shown by the reports from one clinic where this precaution is observed, well justifies it. If no placenta praevia is found a bivalve speculum should be inserted to inspect the cervix. If placenta praevia is found there may be further and profuse bleeding following the vaginal examination. A blood donor must be present as there is no substitute for blood to replace the loss from hemorrhage, and whole blood is indicated.

TREATMENT

The only contribution which the physician can make to the prophylaxis of placenta praevia is to tell patients to notify their physicians when any bleeding is seen. The general principles which govern the *active* treatment are: hospitalization, control of hemorrhage, replacement of blood loss, and termination of pregnancy when the diagnosis is established.

Choice of Method of Delivery.—Two methods of delivery are available, vaginal and abdominal. To decide which is preferable one must weigh several factors. The optimum method is the one which *minimizes* the following hazards: blood loss, trauma with ensuing shock, and infection.

Most writers agree that in complete placenta praevia cesarean section is the procedure of choice. In marginal or partial placenta praevia, to decide the method of delivery one must consider the period of gestation, the viability and the size of the fetus, the parity of the patient, and the condition of the cervix. With a marginal placenta praevia, and occasionally with a partial placenta praevia, when the cervix is soft, partly dilated and favorable for labor, the baby may be delivered through the vagina. However, when the cervix is firm, unfavorable for labor and relatively closed, the abdominal route is preferred.

Vaginal Delivery of the Infant.—There are several methods to consider when one decides upon vaginal delivery:

1. *Rupture of the Membranes.*—This, the simplest method, allows the presenting part to fit against the placenta

and control the bleeding. It may be combined with the use of the Willett[10] clamp on the baby's scalp to keep pressure against the low implanted placenta; or, in case of a breech, one foot may be brought down and used as a tampon. In some of these patients small amounts of pituitary extract, beginning with 1-minim doses, may be administered to start uterine contractions.

The Willett forceps (Fig. 58) is a modification of the T-shaped de Martel scalp clamp, and was introduced in England in 1925. After rupturing the membranes this clamp is fastened to the baby's scalp and gentle traction is applied to keep it against the placenta and cervix. While this clamp has not been used in the clinics with which the writer is associated, Davis[3] reports favorably on its use at the Chicago Lying-In

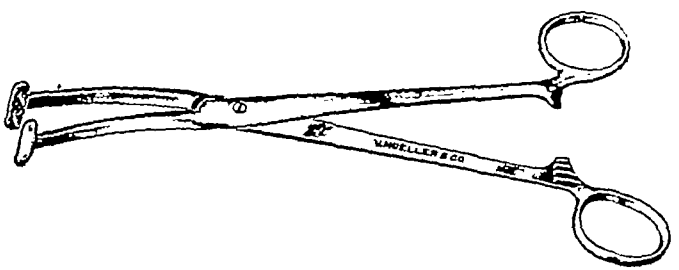

Fig. 58.—Willett scalp obstetrical forceps.

Hospital, and the reports in the contemporary English literature are most favorable. Davis states that the scalp injury may be disregarded.

Sometimes by external version it is possible to convert a vertex to a breech before rupturing the membranes in order to provide a leg for a tampon.

If either of these combinations is employed, it must be remembered that dilation of the cervix requires time, and neither undue pressure nor manual effort to hasten it may be used. Furthermore, delivery must not be attempted until the dilatation is complete.

2. *Metreurysis.*—Metreurysis is not as popular today as it was ten years ago. However, the Voorhees bag is still used in some clinics when artificial rupture of the membranes fails to control the bleeding.

There are two methods of inserting a bag: (*a*) For *intra-ovular insertion* the membranes are ruptured and the bag is placed against the fetal side of the placenta. The disadvantages of this method are infection of the amniotic sac, and increased fetal anoxemia from interference with the placental circulation. (*b*) For *extra-ovular insertion* the bag is inserted into the lower uterine segment without rupturing the membranes. This method may cause premature separation of the low implanted placenta. The writer prefers the intra-ovular method.

The bag must be perfectly filled and a light, steady weight of 250 to 500 gm. must be applied for traction; intermittent pulling should not be countenanced because of the risk of tearing the cervix. A No. 4 or No. 5 bag must be used.

3. *Braxton Hicks Version.*—This has been used less in recent years. It is a valuable method when the baby is small and its viability is in doubt. The disadvantages are the necessity for anesthesia, trauma to the baby, and fetal anoxemia from interference with placental circulation. After the leg has been brought down it may be held, but traction must never be made as severe laceration of the lower uterine segment may result. A review of the mortality statistics shows the dangers of this error.

Methods which meet with disfavor are: tamponade, accouchement forcé, and expectant treatment.

Tamponade to be effective must be done thoroughly; blood clots must be removed and in doing this more bleeding may follow. Furthermore, the danger of introducing infection is a serious one.

Accouchement forcé, by manual or mechanical methods, is mentioned only to be condemned.

Expectant treatment has no place in the care of patients with active bleeding. However, it may be used in the case of patients who have bled but once and stopped, and who have a baby of questionable viability. With such findings the patient must be in bed in the hospital, under the observation of a well trained staff, and with a blood bank or donor available.

In managing the *third stage* of labor, again one should individualize. If the patient does not bleed it is well to wait for separation of the placenta and deliver it in the accustomed

manner. However, if there is bleeding a manual removal of the placenta is imperative, followed by inspection of the cervix with adequate exposure and a good light. Right-angled retractors facilitate exposure of the cervix, and several sponge forceps are essential to grasp the cervical rim and thoroughly inspect it. Repair of any bleeding cervical laceration should be done at once.

One must be aware constantly of the danger of *shock* and try to avoid it by a minimum of trauma, and by treating hemorrhage by adequate transfusions of whole blood.

If the patient is bleeding from the placental site, the uterus and vagina should be packed completely with plain 2-inch gauze. Part of this packing may be removed in twelve hours, and the remainder in twenty-four hours. The writer saw one patient with placenta praevia packed with iodoform gauze who died five days later from iodoform poisoning. As iodoform has little proved value except as a deodorant, plain gauze packing is recommended.

Abdominal Delivery of the Infant.—As previously stated, when a central placenta praevia is found in the last trimester of pregnancy, delivery should be by the abdominal route. With partial placenta praevia and sometimes with a marginal when the cervix is uneffaced, firm, and not favorable for labor, cesarean section is also to be preferred.

The type of cesarean operation used varies with the clinic. Reports of placenta praevia in recent years indicate a trend toward the use of the laparotrachelotomy, in preference to the classical cesarean section. Local anesthesia may be employed in selected cases. Low classical cesarean section may help to avoid the placental site, but laparotrachelotomy affords less risk from infection, the site of bleeding can be packed with greater ease, and there is less likelihood of rupture of the uterus in subsequent labors.

In neglected cases in which the initial warning of bleeding has been ignored and because of lowered resistance the patient has become infected, and especially in those cases in which vaginal packing has been used, a Porro cesarean section may be the procedure of choice.

PROGNOSIS

Kerr,[9] in a review of maternal deaths from placenta praevia before 1930, reported 70 per cent were due to shock and hemorrhage, and 30 per cent were due to sepsis. It is well to remember that the maternal mortality in vaginal deliveries is caused primarily by shock and hemorrhage, while in cesarean sections it is due to infection.

The prognosis is much more favorable now than even ten years ago. I believe that two factors are responsible, namely: (*a*) the earlier and more frequent use of large blood transfusions; and (*b*) the greater frequency of cesarean sections.

Arnell and Guerriero,[4] in reporting 260 cases of placenta praevia at the Charity Hospital, New Orleans, stated that in only 34 per cent of this total were blood transfusions given, but of the patients seen in the last two years, 88 per cent were transfused. At Bellevue Hospital, New York,[1, 2] in the period 1922–32, only 21 per cent of the patients with placenta praevia received blood transfusions, and for the period 1933–38, 50 per cent received transfusions with a resulting decrease in mortality from 11.5 per cent to 2.0 per cent. One death occurred in fifty cases, the patient having been an emergency admission in extremis.

Arnell and Guerriero[4] reported the maternal mortality rate was five times greater when the vaginal route was used than when cesarean section was employed. Likewise the danger to the fetus is about five times greater from the vaginal than the abdominal route. This is easily understood because the majority of the infants are premature and have less chance of surviving the trauma of vaginal deliveries. They reported further that in the first five years only 27 per cent of the cases of placenta praevia were treated by cesarean section. During this period the maternal mortality was 11.3 per cent. In the second five years, 45 per cent of the cases of placenta praevia were treated by cesarean section, and here the maternal mortality was 5.1 per cent.

Siegel,[5] in a study of 332 consecutive cases of placenta praevia at the University of Maryland Hospital and Baltimore City Hospital, reported a maternal mortality of 6.6 per cent in vaginal deliveries, and 1.9 per cent from cesarean section. The fetal mortality was 27.8 per cent from cesarean section and 48.8 per cent in vaginal deliveries.

SUMMARY AND CONCLUSIONS

1. All patients who experience painless bleeding in the last trimester of pregnancy should be placed in a hospital immediately for study and diagnosis.

2. Internal examinations should not be made in the home, nor should vaginal packing be attempted there.

3. Following admission to a hospital the blood should be typed. A complete blood count and cell volume determination are desirable.

4. Blood loss must be replaced early by whole blood transfusions; other fluids are inadequate substitutes.

5. When time permits, roentgenography may be of value for diagnosis.

6. If the patient continues to bleed after admission to the hospital, arrangements should be made immediately for a vaginal examination. However, if the bleeding stops, the patient may be kept in bed for several days before the vaginal examination is made.

7. Vaginal examination should be made in the delivery or operating room, under strict asepsis, with adequate equipment and personnel ready to institute whatever treatment is considered best.

8. The treatment should suit the needs of the individual, and either the vaginal or abdominal route may be used for delivery.

9. The methods recommended for controlling hemorrhage and facilitating vaginal delivery are: (*a*) rupture of membranes alone, or combined with Willett's clamp, or in breech presentations a foot brought down for a tampon; (*b*) metreurysis when indicated; or (*c*) Braxton Hicks version when indicated.

10. Tamponade and expectant treatment are to be employed only rarely.

11. Accouchement forcé should never be used.

12. Two factors have been responsible for the reduction of maternal and fetal mortality in placenta praevia: (*a*) the more frequent and early employment of multiple blood transfusions; and (*b*) the use of cesarean section in selected cases.

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RECENT ADVANCES IN THE DIAGNOSIS AND TREATMENT OF BLOOD DISORDERS IN INFANCY AND CHILDHOOD

IN VIEW of the increasing number of investigations it will be possible to discuss only a few phases of this subject and these have been chosen on the basis of current interest and practical application.

VITAMIN K

Its Isolation and Relation to Prothrombin.—Of the recent advances in hematology none is more spectacular than the discovery of the antihemorrhagic vitamin K. In feeding chicks fat-free diets, Dam observed the development of hemorrhages in various tissues and noted further that this was associated with a lowered clotting time of the blood. It was soon determined that the delay in clotting resulted from a decrease in prothrombin, and that the hemorrhagic tendency resulting from this deficiency could be corrected by feeding substances containing an active principle which was designated as vitamin K. This substance is found in a variety of green plants, notably alfalfa, and in the unsaponifiable, nonsterol fraction of hog liver and putrefied fish meal.

Subsequent studies have shown that bile salts are required for the absorption of vitamin K, and that their exclusion, as in obstructive jaundice, leads to lowered plasma prothrombin and a hemorrhagic tendency. There is evidence also that prothrombin is formed in the liver, provided this organ functions normally and has not been traumatized. Vitamin K may be synthesized in the intestinal tract by bacterial action and

this may constitute an important source of the vitamin for the newborn infant. Reduced prothrombin levels characterize the blood of the normal infant in the first days of life and it has been suggested that, with the ingestion of food and establishment of intestinal flora, vitamin K is produced which in turn increases prothrombin concentration.

Indications for Vitamin K Therapy.—Accumulating evidence confirms the usefulness of vitamin K in the correction of conditions associated with hemorrhage which are dependent upon hypoprothrombinemia. These include *biliary obstruction, various types of hepatic disease, hemorrhagic disease of the newborn,* conditions in which the vitamin K stores have been depleted such as result from *dietary restrictions,* and conditions associated with *poor intestinal absorption.*

In infants and children, the primary indication for the use of vitamin K has been in the prevention and treatment of *hemorrhagic disease of the newborn.* Vitamin K therapy has also been suggested for prevention of reduced prothrombin levels incident to prolonged *diarrheal disorders* or due to periods of starvation sometimes required in their management, or possibly in severe *malnutrition* with deficient vitamin intake. It has also been suggested for the control of *intracranial hemorrhage,* since it is not always possible to determine to what extent hemorrhagic disease or the physiologic hypoprothrombinemia of the newborn contributes to the persistence of bleeding or to poor clot formation.

Methods for Prothrombin Determination.—With the more widespread use of vitamin K or of compounds with vitamin K activity, the need arose for methods of determining prothrombin, for use in diagnosis and in control of medication. The routine tests for blood coagulation have been found unsatisfactory for prothrombin determination because abnormalities become apparent only when prothrombin levels are markedly diminished. *Quick's method*[1] for prothrombin consists of measuring the clotting time of oxalated plasma to which an excess of thromboplastin and a definite quantity of calcium have been added. Another method is the so-called *bedside test* of Smith and his associates[2] in which the clotting time of whole blood containing added thromboplastin is compared with normal blood treated in the same manner and expressed as

percentage of the normal. Tests with the use of capillary blood have been devised by Kato[3] and by Quick[4] which are essentially adapted for younger age groups.

The *two-stage titration method* of Warner, Brinkhous and Smith[5] constitutes the most direct and accurate test for quantitative prothrombin that is at present available. While most desirable for research purposes, it is too complex for routine clinical use. With all methods, experience seems to indicate that a hemorrhagic tendency is observed with prothrombin levels of approximately 20 per cent of normal and that values of from 40 to 70 per cent fall within the danger zone.[2]

The Prophylaxis and Treatment of Hemorrhagic Disease of the Newborn.—Many factors involved in the clotting mechanism have been held accountable for the bleeding in this condition. It has become increasingly evident, however, that an abnormal lowering of prothrombin constitutes its most important cause. A number of methods have revealed that from a reduced or nearly normal prothrombin level at birth there was a further drop to lower levels for a period of from two to six days, and a spontaneous return to birth values by the end of the first week. Hemorrhagic disease could be correlated with an abnormal lowering of prothrombin levels already physiologically reduced. In a number of studies it was found that vitamin K was effective in correcting the deficiency of prothrombin and in the simultaneous cessation of hemorrhage.

The form and dosage in which vitamin K is to be prescribed varies a great deal because of the different strengths of commercial preparations. The vitamin is marketed as *vitamin K concentrates* prepared from alfalfa and dissolved in oil.* Compounds with remarkable vitamin K activity have recently been synthesized and the most potent of these is *2-methyl-1,4-naphthoquinone*. This product is now available in oil, in capsules, or in tablet form.† For the prevention and treatment of hemorrhagic disease bile salts need not be administered either to the mother or to the infant. In addition, water-soluble injectable synthetic compounds‡ with vitamin K action

* Klotogen (Abbott) and Vitamin K in Oil (Parke, Davis & Co.).

† Kayquinone (Abbott), Proklot (Eli Lilly & Co.), Thyloquinone (Squibb) and Quiho-Thrombin (Lederle).

‡ Hykinone (Abbott) and Synkanim (Parke, Davis & Co.).

are now available for use parenterally, including the intravenous route.

To prevent the disease in the newborn, increased prothrombin levels have been obtained following oral administration of 0.5 cc. of vitamin K concentrate (Klotogen) or 0.5 mg. of the product 2-methyl-1,4-naphthoquinone on each of the first three days of life.[6] For the treatment of active bleeding the oral administration of a single dose of 2 cc. of the vitamin K concentrate, or of 1 mg.[7] to 10 mg.[8] of the more potent 2-methyl-1,4-naphthoquinone has been effective. With serious bleeding, parenteral treatment is desirable and fractions to 1 mg. of the naphthoquinone injected intramuscularly have been found efficacious in controlling hemorrhage and in elevating prothrombin.[9]

Vitamin K in the form of the concentrate or of the synthetic product has been administered *to the mother* during the last weeks of pregnancy, just before the onset of labor and even during delivery. It has been shown[10, 11] that the low plasma prothrombin levels at birth are lower in the premature than in the full-term infant, but that these levels could be raised by feeding vitamin K preparations to the mother before delivery. Here, too, the dosage is arbitrary. One of the schedules calls for 1 cc. of natural vitamin K concentrate or 1 mg. of 2-methyl-1,4-naphthoquinone administered daily to the mother in the last ten days of pregnancy.[6] Fitzgerald and Webster[12] found that four capsules of vitamin K concentrate (Klotogen) in a single dose during labor, or 2 mg. of the synthetic product given intravenously, resulted in increased prothrombin in the cord blood and in the maternal blood at the end of labor.

Until recently, the most satisfactory treatment of hemorrhagic disease of the newborn consisted almost entirely of *transfusion* of blood by the intravenous route. The favorable effects of transfusion result not alone from the replacement of cells but also of prothrombin and of other factors contained in the plasma whose deficiency may contribute to the pathogenesis of the hemorrhage. It is possible that there may be other clotting defects besides deficient prothrombin as well as a deficiency of a factor controlling the integrity of blood vessels. The most effective plan of treament at present would seem *the*

combination of vitamin K therapy with transfusion, especially where the bleeding is of sufficient intensity to produce anemia.

BONE MARROW EXAMINATION BY STERNAL PUNCTURE

1. As a Guide in the Interpretation of Blood Reactions Following Sulfanilamide and Its Derivatives.—The widespread use of sulfanilamide and its derivatives has necessitated close observation of the peripheral blood because of their toxic effects upon the hematopoietic system. At a time when the need for continued chemotherapy seems most essential, disturbing blood changes may lead to unjustified withdrawal of the drug. While the incidence of fatal agranulocytosis is greater in adults than in children, toxic reactions occur in lower age groups with sufficient frequency to warrant close watch of the blood. Examination of the bone marrow is particularly desirable because this is the site of origin of the myeloid elements and the place where the full extent of damage to the mature granulocytes and their precursors may be examined at first hand.

Peripheral Blood Changes Produced by Sulfanilamide and Sulfapyridine.—Sulfanilamide and sulfapyridine exert a toxic effect on the red cells as well as on the leukocytes. A mild drop in hemoglobin may be observed when these drugs are administered for ten days or more, but this type of slowly developing anemia does not require stopping the drug. In a small percentage of cases, however, an *acute hemolytic anemia* develops in which the red cells and hemoglobin fall rapidly. The earliest signs are noted between twenty-four and seventy-two hours after treatment is instituted and reach a maximum between the third and fifth day. In addition to the anemia, nucleated red cells and immature myeloid cells appear in the circulating blood.

Leukopenia with or without a drop in polymorphonuclear leukocytes may occur early or late in treatment and represents bone marrow injury. In contradistinction to the severe type of hemolytic anemia which occurs early in treatment, the acute and serious form of *agranulocytosis* occurs usually after the fourteenth day, most often between the seventeenth and twenty-fifth days.[13] While acute hemolytic anemia seems unrelated to dosage of the drug, agranulocytosis follows pro-

longed treatment with large quantities. Another effect upon the white cells is the moderate to marked leukocytosis which usually accompanies the acute form of hemolytic anemia but which may be so extreme as to constitute a leukemoid reaction.[14, 15]

Technic of Sternal Puncture.—A satisfactory puncture site for bone marrow aspiration is located in the midline over the sternum at the level between the second and third ribs. A shortened spinal puncture needle is employed which is adapted to the age of the child* and 0.1 to 0.2 cc. of marrow fluid is rapidly withdrawn. The aspirated fluid is expelled on a slide from which a count of total nucleated cells—red and white—is made with 2 per cent acetic acid, and smears are prepared and then stained on slides or coverslips with one of the accepted methods.

Normal Bone Marrow Values.—There is still limited information as to the normal range for total nucleated cell counts, of the differential percentages for each type of cell, of the variability with different age periods and as to the extent of individual fluctuations. Despite these restrictions, certain qualitative and gross quantitative alterations can be ascertained at this time. In a limited experience, counts of approximately 100,000 to 200,000 total nucleated cells per cu. mm. have been noted in normal children, with a higher upper limit for young infants. The following approximate cell percentages, based on available studies and personal experience, may be employed for comparative purposes: myeloblasts, 1 to 5 per cent; myelocytes (including promyelocytes), 10 to 25 per cent; nonsegmented polymorphonuclear neutrophils (including metamyelocytes), 15 to 30 per cent; segmented polymorphonuclear cells, 5 to 30 per cent; lymphocytes, 15 to 25 per cent; and total nucleated red cells, 15 to 30 per cent.

Result of Toxic Effects on the Bone Marrow.—The toxic effects of sulfanilamide and its derivatives on the bone marrow are represented by varying degrees of suppression of granulocytic elements and at times by a diminished total cellular content. A drop in the bone marrow count to less than 100,000

* A 20-gauge, ¼-inch length is used for very young infants, 20-gauge, ½-inch for older infants and young children, and 18-gauge, ¾-inch for older children and adults.

per cu. mm. in children has been regarded as a caution signal in further use of the drug.[16] In fatal cases the bone marrow is characterized by an absence of polymorphonuclear cells and of myelocytes and by an increased proliferation of myeloblasts, lymphocytes and plasma cells. In extreme stages of aplasia, the bone marrow is infiltrated with lymphocytes and plasma cells to the exclusion of myeloblasts. Nucleated cells of the erythroid series may be slightly diminished or undisturbed. The arrest in development may take place in different phases of granulocytic development. In mild injury, both promyelocytes and myelocytes are present, whereas in the severe and fatal type there is an arrest in development at the myeloblast stage with a complete absence of more mature granular cells.

In patients whose blood shows an initial leukopenia before therapy, the count may rise or show a slight drop following the drug. In cases in which the bone marrow reveals the presence of numerous myelocytes and more mature polymorphonuclear cells, therapy need not be discontinued where the need for it is urgent. Repeated bone marrow studies are required, however, to guard against a sudden shift to an immature level. A marked reduction in the more mature elements and an increase in stem cells and in lymphocytes calls for immediate withdrawal of the drug. With recovery, myelocytes make their appearance in increasing numbers and are followed by more mature polymorphonuclear cells.

In cases with a hyperleukocytosis and a leukemoid blood picture, which occur early in treatment in association with hemolytic anemia, the bone marrow reveals an increased or a normal percentage of myeloid elements together with a normoblastic increase. Replacement of the bone marrow by blast cells which characterizes leukemia does not occur in leukemoid reactions. While leukemoid reactions may be produced by sulfanilamide, there is no evidence that the drug is in any way responsible for leukemia. It is possible, however, that chemotherapy may be instituted at a time when the bone marrow is already infiltrated with leukemic cells but when the peripheral blood is free from the disease. The eventual appearance of leukemic cells in the blood is therefore coincidental and cannot be ascribed to chemotherapy.

2. In the Differentiation of Purpuric States and as a Guide to Splenectomy.—Examination of the bone marrow has also proved a valuable aid in the diagnosis of blood diseases in which purpura constitutes a prominent feature. It often reveals the true nature of disturbances such as leukemia and aplastic anemia in which bleeding is an associated phenomenon. In intrinsic hemorrhagic disorders it permits not only an estimate of the reaction of bone marrow to the loss of blood but direct observation of megakaryocytic content and the extent of platelet formation.

Since splenectomy provides an effective form of therapy in purpura haemorrhagica, it is important to utilize every diagnostic facility to select carefully those cases in which this procedure may be employed to greatest advantage. Every effort must be made to exclude cases of symptomatic purpura, as well as atypical hemorrhagic disorders, from the group of chronic idiopathic thrombocytopenic purpura. While it is recognized that thrombocytopenia is not the sole factor in the causation of hemorrhage and that disturbed capillary function may also be involved, nevertheless platelet deficiency represents the most consistent hematologic feature of this disease. Since the circulating platelets are derived from the *megakaryocytes*, it is desirable to examine these cells closely. Quantitative estimations of the megakaryocytes may be readily carried out in the counting chamber and cytologic study in the fixed smear permits the differentiation of the various developmental types.

No definite number of megakaryocytes can as yet be cited for normal individuals in relation to age because such data are still meager. In a limited experience, however, we have found that these cells in normal children usually range from approximately 10 to 50 per cu. mm., and occasionally up to 100 per cu. mm. This estimate should, however, be checked by inspection of the fixed smear to avoid a false impression of megakaryocytic hypoplasia or aplasia. Megakaryocytes are the largest cells of the bone marrow and are readily identified. Mature forms possess a huge lobulated nucleus and lightly staining basophilic cytoplasm containing fine azurophilic granules. Platelets may be observed in the process of separation from the cytoplasm and detached groups are often noted in the immediate vicinity of the mature cells. Immature megakary-

ocytes are also present and these correspond cytologically to early cells of the lymphoid or myeloid series in respect to a nonsegmented nucleus and deeply basophilic cytoplasm. In addition, platelets are rarely observed in association with the most immature cells.

In essential thrombocytopenic purpura, *hyperplasia* of the megakaryocytes has been noted by many observers. This has been regarded as a compensatory mechanism for the increased destruction of circulating platelets.[17] The increase in megakaryocytic content is a striking feature in the counting chamber, and in the fixed smear it includes a preponderance of immature or promegakaryocytes with deficient platelet formation. Following splenectomy a reduction in megakaryocytes to more normal levels occurs, together with an increase in the number of adult forms.[18]

In another group of chronic purpura, however, a different picture is noted, which is characterized by a megakaryocytic *aplasia*. It has been emphasized by many observers[19, 20, 21] that splenectomy is contraindicated in cases in which the bone marrow shows a marked diminution in megakaryocytes. Failure of improvement after splenectomy has been correlated with depletion of megakaryocytes in the bone marrow. Sternal puncture constitutes, therefore, an essential procedure whenever splenectomy is contemplated.

Acute thrombocytopenic purpura occurs more commonly in infants and in children and the chronic form more generally in adults. In younger age groups etiologic factors include infection, drugs, allergic agents and nutritional deficiency, although many cases remain idiopathic. In childhood, however, the disease tends usually to be self-limited, recovery is customary and recurrence is unusual although the cases of chronic purpura may find their inception at this period.

The following case is typical of thrombocytopenic purpura in childhood and demonstrates the fluctuation in megakaryocytes during the course of the disease:

CASE I.—J. La R., a boy aged three years, was first seen on December 29, 1939, following an acute onset of diffuse purpura two days previously. Marked hematuria occurred shortly before admission. Blood studies showed no anemia, the platelets numbered 36,000 per cu. mm., clot retraction was absent and the tourniquet test was positive. Bone marrow aspiration on December 30, 1939,

showed 255 megakaryocytes per cu. mm., with a preponderance of immature forms. On January 4, 1940, without treatment, the platelets rose to 120,000 per cu. mm. By January 10, 1940, clot retraction began in one hour. On February 16, 1940, the megakaryocytes numbered 61 per cu. mm. and these were mainly mature forms with active separation of platelets. Eight months later the platelet count was 404,000 per cu. mm. and the purpura had not recurred. The tonsils which were regarded as the seat of infection and probably the causative factor in the attack of purpura were removed without complication.

In another patient, a girl of twelve years, with the same condition, the megakaryocytes dropped from 288 per cu. mm. to 33 per cu. mm. in the course of recovery.

3. In the Diagnosis of Hereditary Pseudohemophilia (*Constitutional Thrombopathy; von Willebrand's Syndrome*).—Pseudohemophilia represents one of the better known conditions in the miscellaneous group of atypical hemorrhagic disorders whose clinical and hematologic features are intermediate between purpura and hemophilia.[22, 23, 24] It is a familial hemorrhagic disease occurring in both males and females and is characterized by a tendency to bleed from mucous surfaces, easy bruising, prolonged bleeding time, normal coagulation time and clot retraction, and a normal number of platelets. The tourniquet test is frequently positive but this finding is not consistent. While purpura also occurs, recurrent hemorrhages from the nose and mouth, especially epistaxis, are more common and more severe. Bleeding is first noted in infancy and in early childhood and usually continues into adult life.

Two children with this condition were observed by us. In one, a family history was obtained in two members of the family, but in the other it was absent. In the sporadic cases of hemophilia a familial incidence is also lacking.

Examples of pseudohemophilia are illustrated in the following reports:

CASE II.—D. M., a boy three years of age, was admitted to the hospital with a history of severe epistaxis of nine months' duration. Bleeding from the mouth and into the skin was less marked. Examination of the blood showed a moderate anemia which was corrected by transfusion. The white cells were normal. The platelets numbered 308,000 per cu. mm., the bleeding time ranged from thirty minutes to over one hour. The coagulation time was six minutes and retraction of the clot began in one hour and was complete within a short period. Prothrombin (method of Warner, Brinkhous and Smith) was 100 per cent of normal, and the ascorbic acid content of the plasma was 0.82 mg. per cent which is also within the normal range. Bone marrow aspiration showed

22 megakaryocytes per cu. mm. The majority were mature, with normal separation of platelets. No family history could be obtained.

CASE III.—In this instance the boy was two and one-half years of age and gave a history of bleeding since three months of age. Two of the father's brothers had severe epistaxis in youth, which gradually diminished as they grew older. The blood findings in this patient were similar to those of the preceding one.

Obviously, in these cases bone marrow aspiration was important in eliminating primary diseases associated with abnormal bleeding. Furthermore, it demonstrated that the bleeding could not be explained on the basis of hypoplasia or aplasia of megakaryocytes. While a qualitative defect in the platelets may be concerned in pathogenesis of this disease, it would seem plausible in these cases at least to consider a primary vascular disturbance. The necessity for correct diagnosis of this condition is reflected in the emphasis on conservative treatment. It has been pointed out[23] that the danger of death from hemorrhage precludes elective surgical procedures such as splenectomy. Transfusions represent the most beneficial form of therapy during periods of active bleeding.

4. In Diseases of Lipoid Metabolism, Hemolytic Anemias and Hodgkin's Disease.—In diseases of abnormal lipoid metabolism the sternal smear reveals the diagnostic *Gaucher's cells* characterized by striated or fibrillar network in the cytoplasm, or the typical *foam cells* of Niemann-Pick's disease. Sternal aspiration may assist in clarifying the early diagnosis of hemolytic jaundice and of Cooley's anemia by the pronounced cellularity of the bone marrow in which normoblasts constitute over 50 per cent of all cells.

In two cases of proved Hodgkin's disease the bone marrow showed the characteristic eosinophilia of this condition and in addition an increased number of megakaryocytes. The latter represents an interesting finding in view of Medlar's suggestion[25] that this cell is primarily involved in the pathology of Hodgkin's disease.

THE ROENTGENOGRAM IN DIAGNOSIS OF BLOOD DYSCRASIAS

Leukemia.—*x*-Rays of the skeletal system reveal characteristic changes in certain of the blood dyscrasias and have

served as a valuable diagnostic aid. Their greater usefulness in earlier periods of life than in the adult can be related to the developmental features of the bone marrow. In the infant and

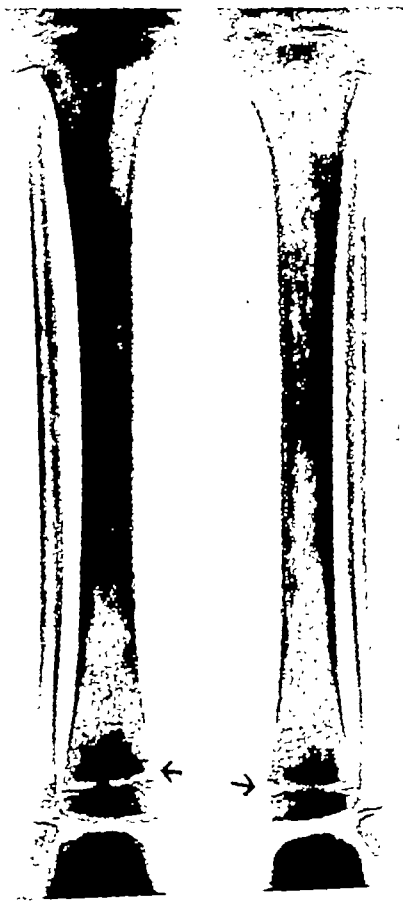

Fig. 58a.—J. P., five years old. Lymphatic leukemia diagnosed early in course as rheumatic disease. Note multiple areas of rarefaction in medullary portion of bones. The arrows point to the narrow transverse zone of diminished density at lower ends of tibiae described in the text.

young child all the bones are filled with red marrow. Only with the appearance of nonfunctioning yellow marrow in the older child and its extension in the young adult is a potential reservoir

created for blood formation when the demand for blood regeneration is increased.

The encroachment upon actively functioning marrow by leukoblastic cells within the bony skeleton at a period when nonfunctioning yellow marrow is not yet available accounts for the roentgenographic changes in this disease.[26] Leukemia in childhood for a considerable period of its course is often not accompanied by enlargement of the spleen or lymph nodes, or by a leukocytosis, and during this time abnormal cells may not be present in the peripheral blood. As previously mentioned, the bone marrow may, however, be extensively involved at a time when characteristic clinical and hematologic features are absent. The roentgenogram, however, throws light upon the underlying pathologic process and discloses generalized or local rarefaction, focal areas of bone absorption and periosteal elevation.

An additional diagnostic feature observed by Baty and Vogt[27] in childhood leukemia is a narrow, transverse zone of rarefaction just proximal to the metaphysis of the long bones, most marked in the lower ends of the femora and tibiae (Fig. 58*a*). This line may be observed in other conditions, but we have found it a valuable diagnostic aid, particularly when leukemic cells are not yet greatly increased in the peripheral blood.

Hemolytic Anemias: Erythroblastic (Cooley's) Anemia, Hemolytic Jaundice, and Sickle Cell Anemia.—Excessive erythrogenesis in younger individuals results in bone marrow expansion, with absorption and atrophy of bony trabeculae and of the cortex. This pathologic process may be sufficiently extensive to be reflected in the roentgenogram. Erythroblastic (Cooley's) anemia, hemolytic jaundice and sickle cell anemia are regarded as constitutional hemolytic anemias and in active stages of these diseases the bone marrow is hyperplastic. Recent case reports have shown that the roentgenographic appearance of the skull and long bones in hemolytic jaundice[28, 29] and in sickle cell anemia[30, 31] is similar to that in erythroblastic or Cooley's anemia. Marked skeletal changes appear with greatest regularity, however, only in Cooley's anemia. The pathologic and roentgenographic alterations to be described in this condition will apply, therefore, to the other members of the hemolytic group.

The separation of erythroblastic anemia from the miscellaneous group of von Jaksch's anemia by Cooley has brought to light many children suffering with this disease. Cooley's anemia, which occurs with few exceptions[32] in children of Mediterranean parentage, reveals both striking hematologic and skeletal changes. Hyperplasia of the bone marrow results in osteoporosis, cortical thinning and an increased width of the medullary cavities. The earliest signs are observed in the small bones, particularly in the metacarpals and metatarsals. Trabeculation occurs especially at the ends of the diaphysis of the long bones, and a common finding consists of atrophy of the cortex with delicate interlacing striations in the distal end of the humerus and proximal portions of the ulna and radius.

Depending on the severity of the disease and the period of clinical onset the skull also reveals variable grades of involvement. In moderate or severe cases the calvarium is greatly thickened, the tables are widely separated, and the outer one may be thinned and atrophied. Lateral views of the skull show an enlarged diploic space which is either finely granular and mottled or striated. The vertical striations or trabeculae have been described as "hair standing on end" and as "brushlike" and appear to extend beyond the outer table.

The greatest opportunity for skeletal changes is in the soft and elastic bones of the infant and least in older children, so that the extent of alteration in the skull and long bones varies with the time of onset. In cases with late onset, long bone changes may be present with only slight skull abnormalities. The initial osteoporotic process occurring in infancy and early childhood is succeeded by osteosclerosis in which new bone is formed and is represented in the roentgenogram by trabeculation and coarse reticulation. Osteosclerosis with cortical thickening in the long bones constitutes an outstanding feature of sickle cell anemia in adults,[30] although its evolution from a previous osteoporotic phase has not frequently been noted.

The roentgenographic features observed in active stages of Cooley's anemia are extremely variable and constant reference should be made in this disease as well as in other hemolytic anemias to the concomitant changes in the peripheral blood. Since Cooley's anemia in mild form seems more widespread than was formerly considered, brief mention should be made of a few recently reported hematologic features.

THE TARGET CELL IN COOLEY'S ANEMIA

Just as the spherocyte is the diagnostic cell in hemolytic jaundice and the sickle cell in sickle cell anemia, recent studies

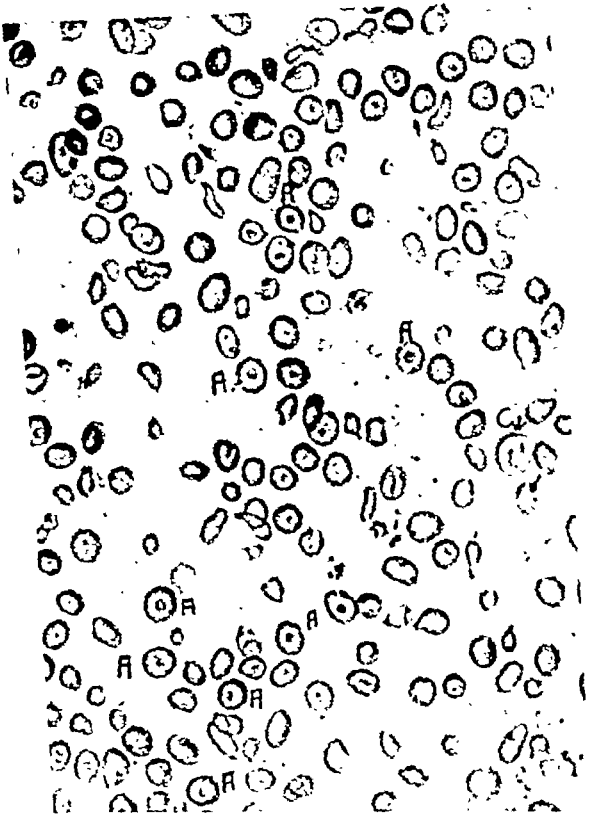

Fig. 59.—N. P., eighteen months old. Blood smear in a case of Cooley's anemia of moderate severity (× 320). Erythrocytes marked *A* are target corpuscles. Note concentric dark and light zones. The central, dense, dotlike area is sometimes connected to the periphery by a band of hemoglobin. *C*, Macrocyte with irregularly clumped hemoglobin with surrounding unstained area. This type of cell becomes more numerous in advanced stages of the disease. Many of the cells in this smear manifest the thinness characteristic of this condition.

have referred to distinctive red cells in Cooley's anemia. While hematologic and roentgenographic changes are marked in advanced cases of Cooley's anemia, diagnosis in early infancy or in mild cases occurring in older individuals is attended with

difficulty. It is possible that in this country there are many with mild or latent forms of this disease who may perhaps be suffering with an unexplained low grade chronic anemia.

Nucleated red cells that characterize established cases and which are especially numerous after splenectomy are absent in early or mild cases. Certain macrocytic red cells found in the blood of advanced cases of Cooley's anemia should, however, be looked for in the smears of early or suspected cases. We had previously pointed out[33] in the blood of infants and children with this disease a type of red cell which was originally described by Barrett[34] as a *target cell.* This red cell has since also been observed in the blood of affected young adults.[35, 36] The target corpuscle was designated as such by Barrett because of its deeply stained center and periphery arranged in concentric light and dark zones (Fig. 59 *A*). It is nonspecific because it may be noted in a variety of conditions, notably in sickle cell anemia and in obstructive jaundice, but its appearance in a macrocytic cell is more suggestive of Cooley's anemia.

A more diagnostic cell is the *large, pale erythrocyte* (Fig. 59 *C*) pointed out by Cooley, which contains irregularly distributed clumped hemoglobin and whose intervening areas seem to possess staining defects. In the early stages of Cooley's anemia and in mild or arrested cases in young adults, however, only a few of each or a single type of cell may be found, but their recognition aids in the diagnosis. The abnormal thinness of the red cells in this disease probably accounts for the increased resistance to hemolysis in dilute saline solutions exhibited by the blood of patients with this disease. This prolonged fragility span may also be noted in the blood of healthy adult relatives.

SUMMARY

Those hematologic advances that are related to the diagnosis and treatment of a few of the more important blood disorders in infancy and childhood have been reviewed in this brief survey. These include the introduction of new methods such as the detection of states of hypoprothrombinemia and the correction of this deficiency by vitamin K, and the examination of the bone marrow by sternal aspiration.

The latter has been employed to advantage in analyzing the

injury produced by the newer chemotherapeutic agents on hematopoiesis, and as a guide in the differentiation of purpuric states and in the choice of cases for splenectomy. Sternal puncture serves also as a diagnostic and confirmatory aid in a variety of blood dyscrasias such as leukemia and pseudohemophilia, in diseases of lipoid metabolism and in some types of Hodgkin's disease.

The roentgenographic changes in leukemia and in the hemolytic anemias, and the discernment of finer morphologic details of diagnostic blood cells occurring in Cooley's anemia, are also described.

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RECENT ADVANCES IN THE DIAGNOSIS AND TREATMENT OF ACUTE POLIOMYELITIS

HISTORICAL BACKGROUND

A BRIEF reference to the historical development of our knowledge of poliomyelitis may be of interest.

More than a century has passed since poliomyelitis was established as a clinical entity by Heine.[1] In spite of, or rather
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were diagnosed. In
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a cerebral type of
notor irritation may
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terioration. I think
that none of us who have seen epidemics of poliomyelitis has observed this type of case; neither have such after-effects been noted in institutions for the after-care of paralyzed patients.

In 1896 Caverly[3] first called attention to the *nonparalytic type* of poliomyelitis. This type was further studied in 1905 by Wickman,[4, 5] to whom, as a matter of fact, credit is often given for first observing it.

For years the terms *abortive poliomyelitis* and "nonparalytic poliomyelitis" were used interchangeably. In fact, this is sometimes done at the present time. Caverly,[3] Wickman[4] and others suspected the existence of a very mild, truly abortive form of the disease with no clinical signs of involvement of the central nervous system—not even the signs of meningeal irritation or the changes in the spinal fluid that usually occur in the nonparalytic type—but it was not until 1931 that the existence of this abortive type was proved by Paul and Trask.[6] In an outbreak of poliomyelitis in Connecticut they were able to demonstrate the virus of poliomyelitis in the nasopharynx of certain children, suffering from a mild febrile illness with gastro-intestinal or anginal symptoms. Moreover, by comparative neutralization studies of the serum at the time of the acute illness and at a later date they showed that the neutralizing power of the serum had increased following the illness. Of course, cases of this abortive type can be definitely diagnosed only by laboratory methods too expensive for general use, but the recognition of its existence is important, especially from the epidemiologic standpoint.

From this brief description we can see how the conceptions of poliomyelitis have developed over a period of nearly a hundred years, from a disease attacking the anterior horn cells of the cord, with a resulting flaccid paralysis, to a disease that may involve various parts of the central nervous system, or that may give rise only to signs of meningeal irritation—the nonparalytic type—or that may be so mild as to escape diagnosis entirely unless recourse is had to extensive laboratory studies.

Space does not permit reference to the outstanding and well known work done in developing the etiology of the disease, to the status of neutralizing antibodies in the serum, or to the extensive studies on immunology and pathology.

TRANSMISSION OF THE VIRUS: EXPERIMENTAL STUDIES

Attempts to transmit poliomyelitis to experimental animals other than the monkey have been uniformly unsuccessful. Recently, Armstrong[7] reported the successful transmission to eastern cotton rats of a strain of virus isolated from a case of poliomyelitis which occurred in Lansing, Michigan, during the summer of 1937. After adaptation to the eastern cotton rat, the Lansing strain was then carried through twelve generations

in white mice.[8] Cotton rats were uniformly susceptible to intracerebral injections but could not be infected by the intranasal route. Upon intracerebral injection, monkeys receiving the brain and cord of infected cotton rats developed severe clinical and pathologic poliomyelitis in all cases.

Jungeblut and Sanders[9] tried to infect cotton rats with five recognized strains of monkey poliomyelitis virus. They obtained negative results with four strains, but with one, the SK New Haven strain, they were able to infect cotton rats and subsequently mice. Attempts to infect monkeys with the virus after it had been passaged through cotton rats were inconclusive. Mice were uniformly infected by the intracerebral route and developed complete flaccid paralysis of the hind legs within three or four days, followed by generalized paralysis and death.

Contrary to Jungeblut and Sanders, Toomey and Takacs,[10] working with nine strains of poliomyelitis virus, could not infect cotton rats with the SK strain. Flexner's MV strain was noninfectious for cotton rats when injected in the usual manner, but when a ten-day colon-typhoid-paratyphoid toxic broth filtrate was added to the virus, paralysis and death were produced in all the rats in the sixth and seventh generations of transfer in these animals. In the sixth and eighth generations the virus was passed from rats to monkeys, producing the disease, and also from monkey to monkey, but not from monkey to rat.

Thus, although it may be possible to infect cotton rats with poliomyelitis virus, it is apparent that much work must be done before it can be definitely established what relationship there is, if any, between these experiments and human poliomyelitis virus.

PORTAL OF ENTRY OF THE VIRUS

The portal of entry of the virus is still a hotly debated question. One school, perhaps the larger, believes that the virus enters the central nervous system directly from the *nasopharynx*, particularly by the olfactory nerve. If this is true, then we must assume that the early symptoms are due directly to the action of the virus on the various parts of the central nervous system. Another school believes that the *digestive tract* is the major portal of entry. This school is divided into two groups, one of which believes that the virus travels directly

by way of the sympathetic fibers into the central nervous system. According to this group, also, the disease is essentially one of the central nervous system. The second group believes that the virus is more or less generally distributed before it localizes in the central nervous system and that the early symptoms are due to the general invasion.

Personally, I am inclined to ally myself with the school which believes that the virus, as a rule, at least, enters the central nervous system from the nasopharynx. Certainly, the finding of the virus in the gastro-intestinal tract does not prove it to be the portal of entry. The virus may just as well have been swallowed from the secretions in the nasopharynx. Trask, Vignec and Paul[11] have recently demonstrated the virus *in the stool* of an abortive case of poliomyelitis twenty-four days after the onset of the mild illness. The authors state that they do not imply that the virus necessarily enters the body by way of the gastro-intestinal tract, but they do emphasize the importance of the feces as a method of exit. "Such facts suggest that during an epidemic of poliomyelitis these common, mild and often unrecognized forms of the disease may be responsible for a high degree of pollution of sewage with poliomyelitis virus."

Evidence that this may be so was subsequently furnished by Paul, Trask and Gard[12] who detected the virus of poliomyelitis in samples of sewage taken during two out of three large urban epidemics of the disease. In one case the virus was repeatedly isolated. Of interest is the fact that, in both instances in which the virus was isolated from the sewage, this was in the vicinity of isolation hospitals.

CLASSIFICATION

We have tried to make a simple classification of the types of poliomyelitis as follows:

1. The *abortive type,* which cannot be diagnosed except by elaborate experimental studies.
2. The *nonparalytic type.*
3. The *lower motor neuron type,* including both spinal and bulbar forms.
4. The *encephalitic type*—rare.
5. The *ataxic type*—very rare.

Occasionally *mixed types* occur.

EARLY SYMPTOMS AND COURSE

From our somewhat limited knowledge, since one can seldom trace the exposure, it is probable that the *incubation period* is rarely less than six or more than eighteen days. Usually it is from seven to fourteen days.

The initial symptoms are much the same in all types of the disease, except the abortive, and they may be quite as severe in the nonparalytic as in the paralytic forms. While the *onset* may, rarely, be insidious, in the vast majority of cases it is very abrupt. Three types of onset may be described. In a somewhat small number of cases, paralysis develops without premonitory symptoms. In another rather small group of cases, there is a period of remission in the development of the disease. In by far the largest group, the symptoms progress rapidly and uninterruptedly.

The early symptoms are *headache, fever, vomiting, constipation* or *diarrhea,* and not infrequently *congestion of the throat and pharynx.* The temperature may be as high as 104° or 105° F. More often it is from 100° to 103° F. It has no characteristic curve. It usually lasts from four or five to ten days or more and generally falls by lysis. Occasionally a secondary elevation of temperature occurs, often but not always accompanied by an extension of the paralysis.

The *pulse rate* is usually in proportion to the fever. A much more rapid rate may indicate an early bulbar involvement and it has been our observation that such a rate not infrequently forecasts a poor prognosis.

Hyperesthesia is often an early symptom. This hyperesthesia may be quite general and elicited by the lightest touch, but it is usually more marked along the spine and over the large nerve trunks and is demonstrated by somewhat deep pressure. Diminution or loss of sensation almost never occurs. *Pain* is an almost constant symptom of the early stages. *Headache* occurs in a large percentage of cases. There is often pain in the neck, back, extremities or abdomen. The abdominal pain sometimes suggests appendicitis. The severity varies greatly. Occasionally sedatives or even opiates are necessary to control it. The duration is usually short, but in some instances the neuritic pains may persist into convalescence.

A symptom-complex of some value is *drowsiness alternating*

with irritability when disturbed. Occasionally this drowsiness may progress to a state of semistupor lasting for several days.

Delirium, on the other hand, is rare in poliomyelitis. *Tremors* or *twitchings* of groups of muscles are occasionally early symptoms. *Ataxia* occurs in rare instances. Convulsions are very infrequent. Meningeal symptoms occurring early are: anteroposterior *stiffness of the neck and back;* often a moderate *Kernig's sign,* and *Brudzinski's* and *Macewen's signs.* The stiffness of the neck and back was noted by Caverly[13] in 1894 and the importance of this symptom has been emphasized by numerous writers since that time. Although usually less marked than early in meningitis, it is probably due to the same factor, namely, an inflammation of the meninges over the posterior nerve roots, which causes pain when the spine is flexed.

Changes in the reflexes are important. Early in the disease the deep reflexes are usually exaggerated and equal. At times a Babinski or an ankle clonus may be present temporarily. As the disease advances, the deep reflexes may become unequal, diminished or lost, especially if a paralysis is about to develop. The superficial reflexes are present unless there is a paralysis of the underlying muscles. The pupils are usually equal and the pupillary reflexes are almost invariably normal. In the rare instances in which the reaction to light is sluggish, the cause may perhaps be a greatly increased spinal fluid pressure. This occasionally occurs even in cases of meningism.

Rarely there may be *retention of urine,* necessitating catheterization. More frequently there is some difficulty in voiding. In severely paralyzed cases there may be incontinence.

A description of the early symptoms gives a very inadequate picture of the disease. The severity and nature of the symptoms listed varies in different outbreaks, and especially in individual patients. In some patients the meningeal symptoms are particularly marked; in a smaller number, the disturbance of the sensorium; in others, the pain and hyperesthesia; in still others, the tremors, muscular twitchings, and other motor phenomena; and occasionally in others, disorders of the gastrointestinal tract or sore throat.

PARALYSIS

Development and Course.—If paralysis, which is practically always flaccid in our experience, occurs, it most often develops on the second or third day of the disease, except in the "dromedary" type, but it may be delayed until the eighth day or, rarely, later. The percentage of cases, diagnosed with reasonable certainty, in which paralysis develops is usually between 25 and 35 per cent. *Premonitory signs* of an approaching paralysis, such as pain, diminution or loss of the deep reflexes, tremor or twitching of groups of muscles, or weakness, may be present, or the paralysis may develop suddenly without warning. In some instances the paralysis reaches its maximum almost immediately. In others, additional paralysis develops over a period lasting from a few hours to two or three days. In the ascending type of paralysis, resembling Landry's, or in the descending type—both of which usually progress to the involvement of the medulla—the pathologic process may go on for several days, occasionally interrupted by a period of remission.

Very rarely it happens that after a period of two or more weeks of apparent quiescence, the paralysis progresses.

Distribution and Severity.—There is apparently considerable difference in the distribution and severity of the paralysis in different epidemics. It would seem that the muscles of one or both legs are most frequently involved, but any group or any combinations of groups may be affected. The degree of involvement varies from weakness to complete loss of power. Death in poliomyelitis is practically always due to respiratory failure associated with increasing paralysis of the muscles of respiration. It would seem that at times death may be due to *involvement of the vital centers* without the skeletal muscles being involved.

During the latter part of the epidemic of poliomyelitis in New York City in 1931, my colleague, Dr. Emanuel Appelbaum, saw a group of five cases which presented a uniform and unusual picture. After the usual symptoms of onset, apathy developed, together with profound asthenia of the whole body to such a degree that there was difficulty even in eating or speaking. At this stage there was no true paralysis, except an internal strabismus in one patient. While the reflexes were

present early, they were abolished as the disease progressed. The temperatures were only moderately elevated, 101° to 103° F. The pulse and respiration rates were generally rapid and there was definite cyanosis and a moderate degree of dyspnea. After the development of these symptoms—apathy, asthenia, cyanosis, and dyspnea—death occurred in from twenty-four to forty-eight hours, although four of these five patients were placed in respirators. This sudden death would seem to indicate an involvement of the vital centers, because patients suffering from paralysis of the muscles of respiration usually live for a longer time in a respirator. In the outbreak of 1935 other cases of this type were seen but they were milder and recovery took place.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Reference has already been made somewhat briefly to the different types of poliomyelitis. Space does not permit a detailed description of these types. Indeed, they are largely self-explanatory. It does seem necessary to point out, however, that a differential diagnosis between the encephalitic or ataxic type of poliomyelitis and *epidemic encephalitis* can be made with no degree of assurance. It may be also stated that it is often difficult or impossible to differentiate the nonparalytic type of poliomyelitis from the meningeal type of encephalitis or clinically from *lymphocytic choriomeningitis*. The diagnosis of the latter disease may be established by virus studies.

Another disease from which poliomyelitis must be differentiated is variously termed *polyneuritis, neuronitis,* or the *Guillain-Barré syndrome.* Undoubtedly this is occasionally diagnosed as poliomyelitis. It has been well described by several authors, notably Guillain,[14] Gilpin et al.,[15] Cobb and Coggeshall,[16] and others. This disease is characterized by a rather gradual onset, often with a sensation of numbness and tingling in the feet and legs, or pain, and sometimes with other sensory disturbances, but without headache, vomiting, high fever or marked signs of meningeal irritation. Flaccid paralysis develops which may be very extensive but which usually clears up satisfactorily. Guillain claims that a diagnostic sign is idiomuscular contractibility. The spinal fluid picture is quite characteristic. In the cases of this disease that we have seen

the diagnosis has been made on the type of onset, and on the fact that the protein in the spinal fluid increased after the acute stage had been passed and remained at a high level for a long time. The cell count is normal at all times. The two etiologic factors that have been suggested are: (1) a virus, and (2) a vitamin deficiency, probably of B_1.

Atypical Outbreaks.—Two rather interesting outbreaks of a disease considered by some authorities as poliomyelitis but presenting certain unusual features occurred not long ago. One was in the summer and fall months of 1935 in Philadelphia. During that period there were undoubted cases of poliomyelitis in and around Philadelphia. The most comprehensive report was made by Lucchesi,[17] who observed the disease both in children and adults. In general, the patients presented the picture of nonparalytic poliomyelitis. Various diagnoses were suggested, such as lymphocytic choriomeningitis or the St. Louis type of encephalitis, as well as nonparalytic poliomyelitis. Indeed, Noone et al.[18] reported the disease as epidemic lymphocytic meningo-encephalitis. Neutralization tests were done with the serums of a number of the patients against the Armstrong virus and the St. Louis virus, with negative results. It is my impression that this was an outbreak of poliomyelitis in which there was a high percentage of nonparalytic cases.

Another outbreak was in Los Angeles in 1934. While this presented certain symptoms suggestive of poliomyelitis, many of them were most unusual, such as involvement of the joints, paralytic ileus, a high rate of infectiousness, especially among the younger nurses and resident physicians. The scope of this paper does not permit a detailed discussion of these outbreaks. They are mentioned merely to show the difficulties encountered in the diagnosis of poliomyelitis at the present time.

Relapses and Second Attacks.—Very rarely, relapses and second attacks of poliomyelitis may occur. By relapse is meant an exacerbation of paralysis several weeks after the disease has apparently become quiescent. A few such instances are reported in the literature and in the epidemic of 1931. Dr. Lawrence Smith[19] described several cases in which an extension of the paralysis occurred from two weeks to two months after the initial attack.

Second attacks of poliomyelitis are comparatively rare.

We have seen six such cases and Fischer and Stillerman[20] have collected records of nineteen more and added one of their own —a total of twenty-six. Doubtless many are not reported.

Examination of Spinal Fluid.—The examination of the spinal fluid is important. In the majority of instances, the spinal fluid is *increased in amount* and shows an *increased cell count* ranging from slightly above normal to several hundred with a high preponderance of mononuclears. In some instances, the polymorphonuclears may predominate and this may occur at any stage of the disease. The *protein* is usually slightly to moderately increased. There is no correlation between increase in cells and the increase in protein. The *sugar* is normal or high. In occasional instances, the spinal fluid findings may be within normal limits. A diagnosis of poliomyelitis cannot be made by the examination of the spinal fluid but certain diseases may be ruled out.

PROPHYLACTIC MEASURES

A great deal of time and study is necessary to evaluate any prophylactic measure in a disease with so low a morbidity as that of poliomyelitis. Another factor to be considered in the utilization of such a measure is that an older age group is now attacked by the disease. Twenty years ago one could confidently state that the period of greatest incidence was between the ages of two and five years. During the past ten years particularly, the period of greatest incidence has extended to the older age groups.

Convalescent Serum and Normal Blood.—One of the first measures to be adopted was the intramuscular administration of convalescent serum or normal adult blood in children known to be exposed. Reasoning from the results with convalescent measles serum during the incubation period (measles also being doubtless a viral disease) there should be some value in this method. However, the protection would be only transient and the results up to date have not been convincing.

Vaccines.—A few years ago, efforts were made to prepare a vaccine to produce immunity. Late in the fall of 1935 the Medical Director of the Public Health Service at Washington advised against the use of poliomyelitis virus for human vaccination. Its use has therefore been discontinued until more

experimental work has been done to prove whether or not a vaccine can be prepared that is acceptable both from the point of view of efficacy and safety.

Vitamins.—Recently the study of the role of avitaminosis, especially of C and B, in susceptibility to poliomyelitis is being pursued. Investigations are also being made as to the part played by the development of certain hormones in susceptibility. Research work has been done recently showing a relationship between certain of the vitamins and certain of the vitamins and certain of the hormones, for example, that vitamin C is elaborated in large quantities in the adrenals. Fascinating as these studies are and important as they may prove to me, it is far too early to warrant a definite statement in regard to their value in either prophylaxis or treatment.

Chemicals Applied to the Nasopharynx.—Chemical blockade has been tried for several years as a method of prevention, on the theory that the portal of entry of the virus is through the olfactory region of the nasopharynx and that the application of certain chemicals would make the mucous membranes impermeable to the virus. The results in experimental work in monkeys have been excellent. In dealing with children during epidemics, the results have not been impressive. For instances, in the epidemic in and around Toronto in 1937, the experiment was carried out on a rather extensive scale. In a group of 4713 treated children, there were eleven cases of poliomyelitis and in a control group of 6300 children, eighteen cases. It was stated also that about 25 per cent of the treated children lost the sense of smell. In most cases this was temporary, but in some, particularly in the older age group, according to the last reports available, the anosmia persisted for a long time.

One may wonder whether these chemicals will prove to be more effective than the well known virucidal effect of the healthy secretions. Furthermore, until some way is found to distinguish the immune from the susceptible, as in diphtheria, this method, or any other, is difficult to apply during an epidemic in a large city. After a rather long experience with meningitis, I have come to have a profound respect for a healthy nasopharyngeal mucosa.

General Hygiene.—The general methods of prophylaxis,

such as avoiding crowds during an epidemic, keeping children in the best possible condition, and so on, are too well known to warrant comment, except that a child well protected in all these ways not infrequently contracts poliomyelitis.

Relation of Tonsillectomy to Incidence.—The high incidence of the bulbar form of poliomyelitis in those who have had recent tonsillectomy and adenoidectomy has prompted Stillerman and Fischer[21] to postulate that poliomyelitis virus can enter the body through the traumatized adenoid and tonsillar tissues. These investigators reported thirteen cases of poliomyelitis occurring ten to twenty-two days following tonsillectomy and adenoidectomy. Of these nine were of the bulbo-encephalitis type.

Sabin[22] has demonstrated experimentally a high incidence of bulbar poliomyelitis in monkeys injected into the tonsillopharyngeal region as compared with those receiving the virus by the nasal route. Additional evidence that the virus did not produce the infection by invasion along the olfactory pathway indicates that after tonsillopharyngeal injection the virus progresses along the local peripheral nerves.

TREATMENT

Convalescent Serum.—The treatment of poliomyelitis continues, in the opinion of most of us, to offer nothing specific. It is still necessary to comment briefly on convalescent serum in the early stages. From 1916 to 1931, a very large majority of physicians in this country and elsewhere had perfect faith that convalescent serum, administered in moderate doses, up to 100 cc., intraspinally, intravenously or intramuscularly before the paralysis set in, would abort the course of the disease and prevent or lessen the paralysis.

From our experience in the epidemic of 1916, those of us in the Meningitis Division thought that the serum did no good, might even be harmful intraspinally in bulbar cases, and that the apparently good results recorded were due to the diagnosis of more and more cases of the nonparalytic type. We[23] wrote a paper expressing our opinions soon after the epidemic. As the years passed and we did not change our views, most physicians thought we were wrong in our original idea and were being obstinate about it. In 1931[24] it was shown that, when approximately 500 cases were treated in the early stages with

convalescent serum, and compared with approximately 500 other cases diagnosed in the early stages but receiving no serum, the outcome in the two groups was essentially the same both with respect to the development of paralysis and to case fatality. Any difference was in favor of the untreated group. These results seem to most of us to be very conclusive clinical evidence that the convalescent serum has no therapeutic value. In addition to this, an experiment indicating that from a purely scientific point of view the serum can have no value was done by Dr. S. D. Kramer.[25]

Dr. Kramer inoculated a number of monkeys with the virus of poliomyelitis and sacrificed them on successive days, some of them before the animals showed any clinical symptoms of the disease. It was found that lesions appeared in the anterior horn cells of the cord some time *before clinical symptoms developed*. This very early invasion of the cells makes it evident that convalescent serum cannot be used sufficiently early to be of any value since it would need to be used before the patient showed any evidence of illness.

More recently some scientists have advanced the idea that if *500 to 600 cc.* of serum were used, good results might be obtained. If they will read the literature of ten to twenty years ago, they will find reports of excellent results where only 20–50 cc. of serum were administered. Moreover, reference should be made to the experiment done by Dr. Kramer which I have just related.

Perivascular Drainage.—Perivascular drainage continues to be advocated by certain workers. It is generally conceded, I believe, that once a virus has been attached to a cell, it cannot be washed off. From Dr. Kramer's work showing that, experimentally, lesions may appear in the anterior horn cells before the monkey develops clinical signs of illness, it would seem, as in the case of convalescent serum, that the treatment to be of value would need to be started before the disease could be diagnosed.

Vitamins.—Reference has already been made to the possibility of using vitamin C or B_1 in treatment and you may remember that I said that the value of either was still problematical. However, I do not see how any harm could result from their use by mouth or parenterally.

Rest.—One method of treatment can be recommended with confidence, and that is complete rest. Its value has been noted for a long time. We have continued to lay emphasis on it since 1916, but in recent years Dr. Philip Stimson,[20] with his clear, emphatic and convincing style, has both in speaking and writing done more than anyone else to bring home to physicians the absolute necessity of this measure in all types of poliomyelitis, even in those that seem mild.

Lumbar Puncture.—Lumbar puncture is often of value, particularly if there are signs of *meningeal irritation* and for what aid in diagnosis the examination of the spinal fluid may offer. It may need to be repeated if signs of meningeal irritation persist. I have seen quite remarkable improvement after lumbar punctures in these cases and I believe that a fairly large amount of fluid should be withdrawn if it seems to be under pressure. In cases of severe *bulbar paralysis*, however, the fluid should be withdrawn with great care, and in the asthenic type which was mentioned earlier, it should not, from our experience, be done at all. The increased pressure or edema of the brain in these cases may be relieved by hypertonic dextrose intravenously once or twice a day.

Respirator.—If respiratory paralysis develops, a respirator should be used. It is well known now that it is useless if bulbar paralysis exists, and even if the patient recovers, there is a high case fatality later from upper respiratory infections, especially pneumonia.[27] No doubt in time more knowledge of the best methods of using the respirator and the after-care of the children will bring about better results.

Feeding; Drainage.—If there is *difficulty in swallowing*, it may be necessary to feed the patient by gavage or by glucose intravenously. In these cases, great care should be taken to keep the throat free from saliva by means of a suction apparatus. It has also been suggested that these patients be turned on the chest with the head lowered so that the secretions may drain from the mouth and nose.

Orthopedic Care.—If weakness or paralysis of any muscle or group of muscles develops, the affected parts must be supported in the proper position by pads, splints or casts as indicated. It is most important even in the early stages that the weakened muscles be protected from attempts at motion or from the tension of the opposing unparalyzed muscles. An

experienced orthopedist should be consulted as soon as any paralysis develops. With proper and prolonged orthopedic care and physiotherapy, excellent results may often be obtained in extensively paralyzed cases.

PROGNOSIS

Although poliomyelitis is by no means to be considered lightly, nevertheless there is a tendency—especially on the part of parents—to overrate its seriousness. There is undoubtedly a large number of cases of the truly abortive type which cannot be accurately diagnosed which confer immunity. Secondly, there is a very large percentage (in the 1931 epidemic about 75 per cent) of cases which can be detected with a high degree of accuracy that develop no paralysis at all. Thirdly, a large number of those patients who do develop paralysis recover with little or no disability if proper and prolonged orthopedic treatment is carried out. Finally, there is no danger of later unfortunate developments, such as behavior disturbances, mental deterioration, or, in the case of older children and of adults, parkinsonism, and other physical disabilities, as there is in encephalitis.

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OTITIS MEDIA

New and Old Methods of Therapy

OTOLOGICAL treatment has kept abreast of progress in other fields of medicine and surgery. Some methods have not withstood the test of time, while new discoveries augment our therapeutic armamentarium. New and old will be discussed in this article on the treatment of otitis media.

Prevention of Otitis Media.—Otitis media is chiefly the result of nasal infection. The prevention of otitis media, therefore, involves the *prevention of colds and sinusitis* as well as the promotion of *nasal hygiene* and proper *nasal ventilation*. Sinusitis should be treated. Nasal obstructions such as adenoids, deviated septum and polyps should be removed. Diving and swimming under water are forbidden. Carefully regulated swimming and perhaps the use of a nose clip to prevent water from entering the eustachian tubes will help to prevent ear infections. Nasal douching should be avoided. The nose should be blown properly with very little force. If there is an obstruction the membranes should be shrunk before blowing. Very susceptible patients with recurrent infections should receive systemic treatment with vitamins, iron and ultraviolet light. Vaccine injections may be tried where the other methods fail.

ACUTE CATARRHAL OTITIS MEDIA (O.M.C.A.)

This condition may be a complete entity or merely the initial stage of acute purulent otitis media. It is manifested by

earache, fever, slightly diminished hearing and redness of the drum without bulging. Inasmuch as it results from acute infection of the nose, sinuses, adenoids or nasopharynx, treatment should be directed principally to these regions.

The most important factor in treatment is *nasal shrinkage* with ephedrine, epinephrine, benzedrine or neosynephrin. The patient should be confined to bed with the head elevated and the room warm and moist. *Steam inhalations* with compound tincture of benzoin are helpful. For the pain in the ear, *analgesics* such as codeine or aspirin are prescribed. A hot water bottle may be applied over the ear. The *local preparations* such as phenol in glycerin, cresatin or auralgan sometimes relieve the earache, but the desquamation of the canal and drum which may result from their use frequently defeats any further effort to examine the drum. When the process subsides, gentle inflation of the eustachian tube aids in recovery of the hearing. Chemotherapy should not be used.

SUBACUTE OTITIS MEDIA

There is a type of otitis media which begins like the acute catarrhal type but thereafter does not act like it or like acute purulent otitis media. The process neither is absorbed nor does it suppurate, but is marked by a hyperplasia which persists. The onset is accompanied by pain and slight fever; these disappear and in their place come deafness, tinnitus and fulness in the ear. Examination even after two months may show a bulging, thickened drum, with complete absence of all landmarks. There may be fluid in the middle ear.

No improvement results from repeated inflations of the eustachian tube. The only remedy for this condition is *myringotomy* under anesthesia, immediately followed by inflation. This treatment usually restores the hearing even after months of impairment, and the fulness and tinnitus soon subside. When untreated, this type of otitis media is frequently the cause of severe permanent deafness.

TRAUMATIC OTITIS MEDIA

This type of acute purulent otitis media is commoner than suspected; it results from secondary infection, following trau-

matic perforation of the eardrum. The usual types of trauma are the impact of water from swimming, diving or waves, air compression from blows on the ear as in boxing or from explosions, burns of the drum from hot metals or liquids, fractures of the skull with involvement of the middle ear, and perforation of the drum by foreign bodies such as cerumen or instruments. These cases have great medicolegal importance; a complete detailed history should be obtained, as the ear injury may be only part of a generalized trauma.

The *symptoms* are bleeding from the ear, discharge, tinnitus, vertigo and deafness. It should be noted that the perforations in the drum are slow and uncertain in healing and the tinnitus very difficult to cure.

Treatment consists first of ascertaining the presence of accompanying injuries. If the skull is fractured the ear canal should not be manipulated or irrigated, nor should the blood clots be removed, lest infection and meningitis follow. If a foreign body is present it should be removed before other treatment is attempted. After the ear has become dry the eustachian tube should be inflated in order to remove any exudate in the tube and middle ear and break up any adhesions which may form. The hearing should always be tested, as a nerve injury may have resulted. It may be advisable to perform tests of the vestibular apparatus.

ACUTE PURULENT OTITIS MEDIA (O.M.P.A.)

Acute purulent otitis media is characterized by persistent earache, redness and bulging of the eardrum. If the symptoms do not subside promptly, myringotomy should be performed.

Myringotomy.—Myringotomy (incision of the eardrum) has completely replaced paracentesis (puncture of the drum) as a method of opening the drum. Paracentesis has been abandoned because it has proved ineffective, it fails to permit proper drainage from the middle ear and attic and necessitates repeated operations.

Technic.—The myringotomy knife with a cutting edge, rather than a sharp needle-like point, should be used and the incision made from below upwards in the posterior part of the drum. This permits adequate drainage from the most impor-

tant areas of the middle ear. The upward incision allows better control of the knife as one works against gravity and away from the canal wall. A rash downward incision will frequently cut the canal wall and if dehiscences are present, especially in an infant, the jugular bulb may be opened with resulting severe hemorrhage. The upward incision should be carried into Shrapnell's membrane, but should not go through the thin tegmen tympani, as meningitis might result. Incision of the canal wall may result in severe bleeding or infection of the wall.

General anesthesia is invariably preferred for myringotomy, except in children under eighteen months. *Local anesthesia* should be used only on adults when general anesthesia is contraindicated or not available. It is usually only partly effective. For local anesthesia equal parts of cocaine, menthol and phenol are mixed and cotton dipped in this mixture is placed against the drum for fifteen minutes.

Indications and Timing.—The advisability of myringotomy and its proper timing frequently pose a delicate problem. There are some physicians who are not in favor of myringotomy at any time but prefer to wait for spontaneous rupture of the drum. The very great majority of otologists, however, do not agree with this practice. Experience with otitis media and its complications soon compels one to favor myringotomy whenever it is indicated. Undue postponement of this procedure leads to complications. Some otologists believe the operation should be done at the earliest sign of acute purulent otitis media. Williams[1] studied a group of cases resulting from scarlet fever, measles and chickenpox and found that early incision of the eardrum gave the best results. It is our belief that each case should be judged individually.

The indications for myringotomy are *earache, fever, headache, sleeplessness, deafness, redness of the drum, bulging of the drum, swelling of the canal wall and mastoid tenderness.* Inadequate drainage from a small, spontaneous perforation may be cause for myringotomy. In small children or infants with high temperature and rapid bulging of the drum, myringotomy should be done early. In adults, unless the pain is very severe, one should wait for bulging of the drum. Myringotomy must sometimes be repeated because of inadequate

drainage or recurrence of symptoms. These cases must be closely observed for signs of surgical mastoiditis. To expect myringotomy always to prevent this condition will lead only to disappointment.

Treatment of the Discharging Ear.—Following myringotomy the patient should be kept at rest in bed and the progress of the infection observed daily. Having once established drainage from the middle ear, every effort must be directed toward maintaining it. If the discharge is thin and drainage is free, *dry wiping* of the entrance of the ear canal can be carried out by a nurse or attendant, using a cotton-tipped toothpick. This procedure should be supplemented by dry wiping of the canal down to the drum on the daily visit of the otologist. After twenty-four to seventy-two hours the discharge may become thick and clotted in the canal, so that the accumulated discharge may act as a mechanical barrier to drainage, even though the myringotomy opening is adequate. In this event we advise *irrigations* with warm normal saline or saturated boric acid solution. These can be safely carried out by patient or attendant by means of an all-rubber ear syringe or a glass return-flow tip attached to a douche bag. When the discharge begins to subside, alcohol and boric drops in the ear aid in establishing antisepsis of the ear canal and prevent invasion by organisms of putrefactive type.

In addition to the direct management of the infected ear, treatment of the nose, nasopharynx and accessory sinuses should not be neglected. We recommend the instillation of 1 per cent ephedrine hydrochloride in normal saline or a 0.25 to 1 per cent neosynephrin solution intranasally every four hours, with the head in the vertex dependent position. If the infection in the ear is preceded or accompanied by purulent sinusitis, we recommend irrigation of the involved sinuses.

Concerning the efficacy of treatment of acute purulent otitis media prior to the use of chemotherapy, Dr. E. P. Fowler, Jr.[2] states that in 963 cases treated at the Vanderbilt Clinic without chemotherapy, 79 per cent of all bacteriologic types of discharging ears dried up in less than four weeks, and 35 per cent ceased to discharge in less than one week.

New Methods of Treatment: Chemotherapy.—The advent of the new chemotherapeutic agents, *sulfanilamide, sul-*

fapyridine and *sulfathiazole,* has extended the horizon in the treatment of acute infections. In their application to the problem of otitis media these questions arise:

1. When should they be used?
2. Should they be used in conjunction with methods already outlined?
3. What change in the clinical picture should one expect with their use in acute purulent otitis media?
4. What constitutes adequate dosage?

In answer to the first question, we believe that they should be reserved for those cases of acute purulent otitis media which are severe in type and which do not respond promptly to the ordinary care which we have outlined. In short, we do not recommend their indiscriminate use. Investigation to date has revealed that sulfanilamide is most effective in the treatment of beta hemolytic streptococcus infections, that pneumococcus infections respond best to sulfapyridine, and that sulfathiazole is better employed in combating staphylococcus infections. In the event that one drug is poorly tolerated, it is advisable to substitute one of the others.

Answering question 2, we must emphasize that the older methods, myringotomy and care of the nose, nasopharynx and the accessory nasal sinuses, are the keystone of rational treatment. The patient should be confined to bed, preferably in the hospital, where the effect of these drugs on blood picture, blood levels and immunologic response can be closely observed and controlled. We condemn the practice of giving small ambulatory doses.

Regarding question 3, the changes in the clinical picture which we have repeatedly observed are, first, the tendency of these new drugs to mask the usual clinical warnings of mastoiditis; and second, to produce toxic reactions, chills and high fever which mimic the picture of incipient intracranial complications.

Dosages.—Adequate dosages of the various drugs, which have been worked out on the basis of blood level concentrations, are described below:

1. Both *sulfanilamide* and *sulfapyridine* should be given on the basis of 0.2 gm. per kilogram of body weight for the first twenty-four hours. The dosage should then be reduced to 0.1

gm. per kilogram as long as treatment is continued. The drug should be given every four hours, day and night, in order to maintain an adequate blood level. Bicarbonate of soda in doses of 0.3 to 0.8 gm. should be given with each dose of the drug.

2. As to *sulfathiazole*, we recommend an initial dose of 0.1 gm. per kilogram of body weight, followed after four hours by a dosage of 0.3 gm. per kilogram for the twenty-four hours, in divided doses. The initial dose should not exceed 2 to 3 gm. and each succeeding dose should not be over 1.5 gm., with a maximum total dosage of 9 gm. in twenty-four hours. Adequate fluid intake must be maintained.

In otitic infections, where one is dealing with probable *bone necrosis*, chemotherapy should be continued beyond the period of apparent clinical cure in order to forfend against recurrence of infection. When the patient does not seem to respond to chemotherapy, his failure to produce antibacterial antibody should be suspected and determined. In these cases immune serum should be administered.[3] In the authors' study[4] of 183 unselected cases of otitis media in children, ninety-three of these received chemotherapy and eighty-eight control cases were treated by the usual methods. In this series it was observed that the duration of the aural discharge was reduced by one third in the group receiving chemotherapy, and the number of mastoidectomies in this group were reduced by about one half.

CHRONIC PURULENT OTITIS MEDIA (O.M.P.C.)

Chronic purulent otitis media is not so common as formerly, probably as a result of the more thorough treatment of acute otitis media today. However, it remains as difficult a problem as ever; nor do the recent chemotherapeutic developments offer much help, owing to the inherent bony necroses involved. The first question to be decided is the *type of therapy*. Should it be nonoperative, minor or major operative? Excluding cases which show symptoms or signs of impending or actual intracranial complications, such as facial paralysis, labyrinthitis, meningitis and brain abscess, treatment should first be medical or minor operative in scope.

Ninety per cent of all patients with chronic purulent otitis

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media treated in the authors' private practice were discharged with dry ears after a period of treatment. Almost all of these were permanently dry. Of those who presented recurrent discharge, almost all responded to another course of treatment. It has been noted that, in clinic practice, operation is much more frequently necessary for this condition.

The *prevention* of chronic purulent otitis media lies in the prevention and proper therapy of the acute purulent disease. All cases which show persistent discharge in spite of careful treatment, including tonsillectomy and adenoidectomy when indicated, should have a simple mastoidectomy performed. Patients with perforated eardrums should not be permitted to swim or dive. Bathing caps or ear plugs should be worn while in baths or showers to prevent the entrance of water into the ear. The nose and sinuses should be properly treated. Infected antra should be irrigated.

The *local treatment* of the ear consists in the institution of a systematic cleansing of the canal and middle ear at regular intervals of three to seven days. This condition is one in which scrupulous attention to detail is the most important factor in success. First, the discharge must be removed, and dry treatment is preferable, although an initial irrigation may be necessary. After this the ear should not be irrigated. Peroxide may be used to remove the discharge and the detritus; the canal and middle ear are now thoroughly dried, preferably with alcohol on cotton.

All *polyps* and *granulations* should be removed with snares, punches and curettes, using local anesthesia with adrenalin to control the bleeding. General anesthesia is not favored because its use increases bleeding and makes visualization difficult. The bases of the growths are cauterized with 50 per cent silver nitrate in small amounts accurately placed. A powder combination of boric acid and iodine is insufflated into the middle ear.

The *home treatment* consists in keeping the nose clean, cleansing the outer canal with clean cotton, and the use of alcohol drops. If discharge persists in spite of conscientious local treatment and the hearing is markedly reduced in the affected ear, radical mastoidectomy should be performed. However, if the hearing is good, the modified radical operation

should be the operation of choice. Although this operation is less apt to produce a dry ear, it at least lessens the threat of intracranial complications, and it preserves the hearing.

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SOME FUNDAMENTALS OF PSYCHIATRY

ALTHOUGH there still exists among many medical men an idea that psychiatry is too complex a specialty to warrant any attempt to acquire a working knowledge of it, the number is fortunately diminishing. Those who have equipped themselves with this knowledge are finding it of material aid in their practice of medicine, especially in communities where there is no psychiatrist and the doctor must necessarily be both physician and specialist. But even in large metropolitan areas where psychiatrists are available, familiarity with the fundamentals of psychiatry is a valuable adjunct to the doctor in the management of baffling complaints and symptoms failing to yield to the usual methods of treatment.

It is the physician who usually has the first contact with the mentally disturbed patient. By training himself in the art of observing accurately every patient's general behavior and reactions, he will not only resolve some of his own difficulties with regard to diagnosis, but will be in a position to help at least a certain number of unfortunate individuals before it is too late. The percentage of cures, particularly in conditions like schizophrenia and general paralysis when recognized early, has risen under modern methods of treatment in our psychiatric institutions.

THE PROPER PSYCHIATRIC APPROACH

More than fifty years ago Spitzka wrote: *To the experienced alienists there is no more suggestive sign of mental disorder than the insane expression, attitude, and manner.*

There is no reason why the average physician as well as the alienist cannot detect deviations from the normal. A careful analysis of the disturbed patient's *history*, as obtained from his relatives and from himself; a study of his *demeanor* while in the office; and a thorough *physical examination* should make it possible for the general practitioner to make a tentative diagnosis of mental disease.

Eliciting the History from a Relative or Friend.—In the majority of cases, the psychosis presents an accentuation or distortion of prepsychotic traits. For this reason, if at all possible, information should be obtained from a relative or close associate of the patient regarding the type of personality with which one is dealing. This is necessary for diagnostic purposes. It is not absolutely essential in medicolegal practice because such facts may be included in a hypothetical question propounded to the expert.

History taking should be orderly, that is, it should progress from one stage of the patient's life to another. Every factor in that life is of importance. Were gestation and birth normal? Did the patient have the usual childhood diseases? Was he considered a "nervous" child? Did he ever have convulsions or epileptic seizures? Did he have any illnesses during adolescence? Did he sustain any injuries during childhood or adolescence? Has he ever expressed fears or a feeling of insecurity? Has he exhibited peculiarities of conduct?

Did he graduate from grammar school? From high school? From college? Was he a good student?

What about his working record? While working, has he applied himself diligently? How many positions has he held? How long did he remain in each? Was he discharged? Did he quit of his own free will?

How does he spend his leisure? Has he any hobbies? Has he many friends? Is he a good mixer?

What about his sex life? How does he satisfy the sexual urge? Does he associate with girls, or prefer boys?

Has the patient had any recent experience leading to frustration of hopes and wishes? Has anything happened to injure his pride? Has some social experience led to disillusionment?

Demeanor.—It is highly essential to note the bearing or outward behavior of the patient. Does he grimace? Does he

fidget? Does he appear to be frightened? Does he glance behind him from time to time?

Emotional reactions are important. Is he sullen? Is he depressed? Is he happy, optimistic and pleasant? Is he silly? What is his emotional tone as he answers questions? Is his emotional response adequate or inadequate? Does he become excited? Is he apathetic?

Physical Status.—The general build of the patient may be significant.

Dementia praecox (or schizophrenia) is most often seen in the *asthenic* and *athletic types*. The asthenic individual (leptosome physique) is delicately built: his chest is flat, his neck and extremities are long, his shoulders are stooped, and there is often visceroptosis. The athletic status is characterized by a narrow pelvis and prominent musculature: the shoulders are broad, the chest is wide, and the hands are large and strong.

Dementia praecox is found, also, in the *dysplastic type* which is characterized by disturbance in function of the glands of internal secretion. Hinsie has subdivided these individuals into three groups: (1) elongated eunuchoids, (2) eunuchoids with fat abnormalities, and (3) individuals showing infantilism and hypoplasia.

Manic-depressive psychosis is most frequently found among those of another type, the *pyknic*. People of this status have a rounded figure with a more or less even distribution of fat: the torso, neck and extremities are short, the abdomen is large, the chest has a large circumference, and the skull is large and round. The skin and muscles are soft and smooth.

Questioning the Patient.—Avoid asking direct questions as much as possible. Although certain patients may be asked direct questions, it is best to accustom one's self to the indirect method of examination and so avoid making suggestions that might influence the patient's answer. For example:

When trying to elicit *hallucinatory manifestations*, do not ask, "Do you hear voices?" If the patient has something to gain by a diagnosis of mental disturbance (as in a court action for head injury in which the patient is the plaintiff), he is very apt to respond eagerly with, "Yes, I hear voices."

When eliciting *delusions*, do not inquire, "Are people trying to harm you?" Instead, ask:

"How do you get along with members of your family?"
"How do you get along with people in general?"
"Have you any friends?"

In a recent investigation, the following line of interrogation was pursued with an excellent response as to both hallucinations and delusions:

Q. "How do you sleep at night?"
A. "I sleep very little."
Q. "Why?"
A. "There are noises that keep me awake."
Q. "What are these noises?"
A. "People calling me names, threatening to kill me, threatening to poison me. I have to stuff the cracks in my door and windows. They introduce poison gas through these."
Q. "Why do they wish to kill you?"
A. "They think I know too much."
Q. "Yes," (sympathetically) "go on."

The entire story followed. In many cases it is necessary to dig and dig; one must never let up.

The answers to questions as to delusions and hallucinations usually reveal evidence of *passivity* feelings (*control by an external agency*). The following case is illustrative:

A woman walked into my office recently to complain of a man who wished to kill her with serum. He would inject her with a needle which gave her a tremor and a constant stiff neck. She never saw him do it, but said she could always see the mark. She didn't know his name.

Q. "How do these needles affect you?"
A. "They make my thoughts clear to him; he can read them and knows just what I am doing."
Q. "What makes you believe that this is so?"
A. "I am always in a daze. He hypnotizes me. He directs all my actions. He wants to kill me."
Q. "Do you ever try to resist doing these things?"
A. "He makes me do them against my will. He even has sexual relations with me in my sleep. I can't do anything about it because he makes me do what he wishes."
Q. "What else does he do to you?"
A. "He gets people to say bad things about me over the radio. I've heard my name mentioned."

It is strange how very often paranoid praecox patients state that they hear their names mentioned over the radio. They

sometimes say that they hear songs which are for their benefit, and may state that their names are mentioned in these songs.

After eliciting information as to hallucinations and delusions, continue questioning for *compulsions*. Useful questions are:

"Is there anything else that bothers you?"
"Have you ever tried to get rid of these ideas?"
"Do you find that you cannot rid yourself of these ideas?"
"Why?"
"These things must have made you very nervous. In what way have they made you nervous?"

The reply usually indicates that the individual cannot attend to his work and cannot make decisions. If this be the case, continue the interrogation:

"Do you feel that you must do things in a certain way?"
"Do you feel uncomfortable unless you do them in this certain way?"

In testing *moods* inquire, "Well, how do you feel today?" Note the patient's reactions and appearance during your interrogation and be guided accordingly. For example:

"You don't seem very happy. Do you always feel this way?"
"Are there times when you feel happier?"
"How do you feel towards life?"

The *orientation* of the patient should be investigated. Helpful questions are:

"What is your name?"
"Do you know what day of the week this is?"
"What month is it?"
"What year?"
"What place is this?"
"Do you know who I am?"

An idea of the patient's *general memory* can be gained during the process of taking the patient's own history as to his family, school and background. *Special memory* may be tested by questions like the following:

"Who is the President of the United States?"
"Who was the President before him?"
"Name the capital of the United States."
"What is the capital of this state?"

There are a number of methods of inquiry into *retentiveness* and *recollection*. One may begin by saying:

> "I am going to give you three things to remember. I shall ask you to repeat them later. The three items are: MRS. JONES, 425 BRIDGE STREET, THIRD FLOOR."

Continue to talk to the patient, or ask a few miscellaneous questions, for three to five minutes. Then ask him to recall the three facts he was to remember. Next ask him to repeat six numbers in the order in which he hears them. (*Example:* 4-2-6-3-9-5, or 8-2-1-6-4-9.) Next, ask him to repeat a sequence of numbers backward beginning with four numbers, then five numbers, and six numbers: (*Example:* 4-1-6-2; 3-5-2-1-8; 1-9-8-4-2-6). Give the numbers slowly and distinctly.

Ask the patient to do simple sums in addition, subtraction, multiplication and division. Give him simple arithmetical problems to solve. (*Example:* You have 50 cents. If you went into a store and spent 5 cents for bread and 3 cents for a newspaper, how much change would you get?)

Give the patient three words and tell him to use them in a sentence. (*Example:* Man, gun, dog, or Boy, water, bucket.)

Now tell the patient a story and ask him to repeat it in substance. *Example:*

COWBOY STORY

A cowboy from Arizona went to San Francisco with his dog, which he left at a dealer's while he purchased a new suit of clothes. Dressed finely, he went to the dog, whistled to him, called him by name and patted him. But the dog would have nothing to do with him in his new hat and coat but gave a mournful howl. Coaxing was of no avail. So the cowboy went away and donned his old garments, whereupon the dog immediately showed his wild joy on seeing his master as he thought he ought to be.

Memory also involves imagery and imagination. A discussion of these is not necessary in this paper.

As a test of *recognition*, give the patient a sheet of paper on which are written three disconnected sentences. Allow him to study each sentence for one second, then remove the paper and give the patient another sheet on which there are listed a dozen or so disconnected sentences including the sentences

previously presented. Allow five seconds for the patient to designate the sentences originally seen.

Present to the patient three cards in sequence on which there appears a nonsense word (*axyct*). Allow one second for study of card. Then present a list of ten nonsense words. Allow ten seconds for recognition of original nonsense word.

Test *judgment* by reading a statement such as:

Bill Jones's feet are so big he has to pull his trousers on over his head.

or

One day a man called at the post office and asked if there was a letter waiting for him.
"What is your name?" asked the postmaster.
"Why," said the man, "you will find my name on the envelope."

After either statement, ask, "What is foolish about that?" If the response is ambiguous, inquire, "Why is it foolish?" For other test sentences see the section on Absurdities in Form L, Revised Stanford-Binet Scale (Terman and Merrill: "Measuring Intelligence").

With regard to *insight*, ask the patient if he has any plans for the future; encourage him to go into detail. If your examination has revealed an abnormal thought pattern, it is advisable to ask the following:

"You certainly must have given these matters that trouble you a great deal of thought. How do you explain your difficulties?"
"Do you think there is something the matter with you?"

If the patient replies in the negative, do not give up.

"Well, if there is nothing the matter with you, what do you think prompted your mother (friend or relative) to bring you to my office?"
"Do you think you are just as well now as you ever were in your life?"

The patient may have *ideas of reference*. He believes that people on the street look at him in a peculiar way. When he passes people talking to one another, he is sure they are talking about him.

Finally, ask the patient if he has any special complaints such as aches or pains. It is possible that these are *hypochondriacal ideas*. If not, the answer may lead to the discovery of a delusional content.

The history given by the patient, the collateral history ob-

tained from relatives or friends, the examination of the patient, and your observations of his demeanor during the examination should enable you to judge the patient's mental status with a fair degree of accuracy. If you will now familiarize yourself with the outstanding features of the most common forms of psychosis you will be well on the way to diagnosing correctly the exact nature of your patient's illness.

SCHIZOPHRENIA
(Dementia Praecox)

Schizophrenia is used synonymously with dementia praecox. The term "schizophrenia" was introduced by Bleuler in 1908, and means "splitting of the mind." It is a mental disorder, most commonly seen in puberty and adolescence, characterized by a splitting of the thought content, a loss of interest in the environment, disturbances in conduct and emotions, and a severance from reality. According to Bleuler, "the thought processes are controlled by groups of ideas that have a strong emotional interest for the personality." There are several forms or degrees of schizophrenia.

Simple:

The onset is marked by an insidious change in personality.
Loss of initiative. The patient may become a vagrant.
Indifference, listlessness, irresponsible and not interested in environment.
Poor emotional tone.
Judgment and insight are usually faulty.
Social maladaptation.
Orientation is not defective.
Memory is usually not impaired.
Intellect is seldom damaged.

Hebephrenic:

Onset: insidious in some cases; subacute in others.
Emotional dilapidation.
Impulsive behavior:
  Periodic excitability in some cases.
Personality disintegration and rapid deterioration:
  Mannerisms.
  Silliness.
  Incoherence.
  Prominent recessive features.
Fantastic ideational processes:
  Ideas of reference.
  Ideas of influence.

Catatonic:

Usually occurs between fifteen and twenty-five years of age; the onset may be acute and is frequently precipitated by an emotional experience.
The patient is noncommunicative or stuporous at one time, markedly excited at another.
If excited:
May present great excitement and agitation.
Impulsive acts frequent.
May be assaultive.
Repeats certain words and gestures over and over.
Speech may be disconnected.
If stuporous, *negativism** is usually present:
Resistant to all movements, refusing to talk, walk or eat.
May tightly close jaws and eyes and clench fists.
May be resistant to all spontaneous motion, but responsive to anyone who starts him walking or moving.
A statuesque attitude may be assumed and retained for a long time:
Masklike facies.
Fixed, blank gaze.
No reaction to painful stimuli.
May drool saliva.
May grimace.
May be unable to control bowel movements and so soil himself.

Paranoid (Typical).—Paranoia and paranoid schizophrenia are not synonymous. Paranoia is a mental disease characterized by a definite system of delusions, with little or no disturbance in clarity of thinking. There is little deterioration and the person may carry on for many years and indulge in a useful life. There may be hallucinations in some cases. Paranoid is an adjective meaning "resembling paranoia."

Paranoid schizophrenia occurs later in life, as a rule, than the other forms of schizophrenia.
The onset is usually gradual, with slow deterioration.
There is severance from reality.
Delusions may be numerous and changeable:
Delusions of persecution are most common.
Ideas of influence may be prominent.
Ideas of reference are occasionally present.
Hallucinations.
Disturbed associations.
Inadequate affect (mood).
Insight: may be poor.
Speech: may be spontaneous, but guarded.
Memory: usually good.
Orientation: unimpaired, as a rule.

* *Negativism:* "A mental state where one suggestion immediately produces a strong counter suggestion in the patient so that he does exactly the opposite of what he is asked or told to do." S. Kahn.

Paranoid (Atypical).—At times one meets with schizophrenics who present manifestations of both the paranoid and catatonic varieties of schizophrenia. Less often the paranoid patient develops paresis or will present senile signs so prominently as to color the picture of paranoid schizophrenia.

The condition may develop in mental defectives; it may also occur in the epileptic person.

Prognosis for Schizophrenia.—With modern treatment, the outlook for the schizophrenic is much better than it was several years ago. Insulin and metrazol have given much hope. Insulin treatment has been responsible for more recoveries than has metrazol. On the other hand, metrazol treatment has produced a greater percentage of improvement in the condition of patients. Electric shock treatment, now being tried, has been effective in certain cases.

As to cure, the catatonic type has been most benefited, with the paranoid form next in frequency; simple and hebephrenic types of schizophrenia have the lowest rating, being almost unaffected by any of the modern methods of therapy.

As to improvement, the catatonic, the simple and the paranoid types run about even; the hebephrenic form shows the poorest result.

The prognosis as to cure depends largely upon the *age* of the patient and the *stage of the disease* at the time treatment is instituted. The younger the person, the better the prognosis; the earlier the stage, the better the prognosis. On the other hand, it as been found that when schizophrenia begins at an age between twenty-five and thirty years and treatment is instituted early, the results are better and there is less chance of recurrence than in patients who are fifteen to eighteen years of age when the disease begins and treatment is immediately instituted.

MANIC-DEPRESSIVE PSYCHOSIS

In this form of insanity, mania and depression may alternate. The term includes simple mania and melancholia, recurrent mania and melancholia, periodic mania and melancholia, and circular or cyclic insanity, which is a state characterized by alternating manic and depressive phases without any quies-

cent intervals. Hereditary and constitutional factors play an important etiologic role.

Manic Phase:

Hypomania: a state of mild excitement; moderate insanity.
The patient shows great self-confidence, is almost always smiling, buoyant, and everything is just fine.
He may suddenly show great anger and become argumentative, abusive and hostile.
He is generally talkative, boastful and flighty, one thought seemingly giving rise to another.
His attention is readily distracted and he lacks insight.
Because of his grandiose feeling and confidence in his ability to do great things, he may plunge recklessly into business ventures with the idea of making much money.
Memory: good.
Orientation: usually good.
Hallucinations: seldom present.

There is a *milder type of hypomania* which is simply characterized by loquaciousness, a feeling of being satisfied with oneself, with no distractability or boastfulness. Insight is present and the person may be gainfully engaged and very successful in his work.

Mania: a variety of insanity characterized by an expansive emotional state such as wild excitement and a tendency to violence; *insanity with exaltation.*
There is fluctuation of mood, from great euphoria to great excitement and anger.
Profanity is not uncommon even in women.
There are delusional trends:
The patient may decorate himself with rags, feathers, medals and buttons.
Ideas are flighty.
Attention is easily distracted.
When explaining something, the patient may go into great detail, without system and frequently using words which sound all right but which have no relationship to each other (clang).
He may be noisy and shout.
If he hurts himself, he may pay no attention to it.
Although sleeping little, he does not seem to be fatigued; there may be loss of weight.
There may be absence of recognition of relatives, or strangers may be mistaken for relatives.
Women may expose themselves and invite sexual intercourse.
Memory is good.
Orientation is seldom affected except in extreme cases.
Intellect: little impairment.

Depressive Phase:

Mild: The patient simply feels out of sorts. His complaints are vague. The appetite is poor. He is sad, feeling physically unable to perform tasks and mingle with people. He may feel that he is neglecting his family. There is lack of initiative and interest.

Relatively severe: The patient may state that he is very ill, that he suffers from some physical illness. His appetite is poor, he is losing weight, and is constipated. He is so fatigued that every motion is an effort; he is too tired to walk and will not do so unless forced. He is extremely gloomy and his tears flow on the least provocation.

If completely depressed, he answers questions in a low tone, without facial expression:

The thought processes are greatly retarded.

Everything seems unreal and there is an overwhelming sense of inferiority.

He suffers from a feeling of guilt because he is completely useless to himself and his family.

At times there is great apprehension; something terrible is about to happen.

There may be fleeting delusions, but hallucinations are uncommon.

Memory is intact.

Orientation is intact.

Severe:

The condition is one of stupor:

The face is expressionless.

The patient will not talk.

He has no interest whatsoever in his surroundings.

He cannot be made to cooperate.

He may soil himself.

Tube feeding may become necessary.

Mixed Forms:

Kraepelin has distinguished six mixed types, characterized by: (1) agitated depression, (2) manic stupor, (3) unproductive mania, (4) depressive mania, (5) depression and flights, and (6) inhibited mania.

Prognosis of Manic-depressive Psychosis.—The incidence of manic attacks is usually every six months; of depressive attacks every nine or ten months. It does not necessarily follow that because an individual has had one episode he will develop others. However, recurrence is particularly common in those who have had an attack early in life. Depressive states are more frequent in adults than in adolescents. Even after several episodes, the mind need not be affected as regards

intelligence. Insulin has had no curative effect upon this form of insanity. Regarding the mild hypomanic, it is at times difficult to decide whether hospitalization is necessary; I believe it inadvisable to make any definite ruling in these cases. At times psychiatrists state that the mild hypomanic state is a forerunner of a true manic condition. Pollock states, in discussing recurrence of attacks, "in more than half of the cases there is no recurrence of attacks of sufficient severity to cause readmission to a hospital for mental disease."

PSYCHOSES DUE TO ALCOHOL

Delirium Tremens:

Onset: acute, characterized by great motor restlessness and delirium.
The pulse rate is increased.
The temperature rises.
Face: usually flushed and perspiring.
Eyes: the conjunctivae are congested, the pupils dilated.
Speech: indistinct.
Tremors of the tongue and fingers.
Ataxia.
Urine: may contain albumin.
Visual, tactile and olfactory hallucinations may be present:
Visual hallucinations are particularly terrifying.
The patient is fearful, apprehensive and unable to sleep.
He is confused and disoriented, with consciousness clouded.
Epileptiform seizures occur in some cases.
The attack may be followed by complete amnesia for the events occurring during its course.

Alcoholic Paranoia:

Accentuation of previous personality defects.
Delusions of infidelity and of persecution.
Suspicious.
Auditory hallucinations may be present.
Sensorium may be fairly clear.

CASE REPORT.—X was forty years of age, a married plumber, the father of two children. He was a chronic drinker. He had always been jealous and stubborn and could not be reasoned with. Family quarrels were frequent. He began to complain that the men with whom he worked were saying things about him. He accused his wife of being untrue, and said that the last child was not his; that he looked like one of the men with whom he worked. He mistreated this child. Unknown to his wife he cut a hole in the door so that he could watch his wife's actions through it. One morning while at the dumb-waiter she spoke to the milkman. X opened the door suddenly, accused his wife of infidelity, and assaulted her. Then he offered to forgive her and continue to live with her, provided she would promise to give up the milkman. He was sent to Matteawan, an institution for the criminal insane. He did not recover.

Korsakoff's Psychosis (*Chronic Alcoholic Delirium*):

Orientation is markedly disturbed.
Confabulation.
Falsification of memory.
Headache and dizziness.
Syncope.
Alternation of mood from anxiety to indifference, irritability and suspicion.
Susceptible to external stimulation and suggestions.
Signs of polyneuritis (wrist drop, etc.) usually present.
Amnesia for events immediate and remote may occur following recovery.

Acute Alcoholic Hallucinosis.—This is a phenomenon of habitual alcoholism precipitated by overindulgence.

Hallucinations, causing great fear and a marked reaction:
Auditory.
Olfactory.
Visual (occasional).
Delusions of persecution and ideas of reference.
Suicide may be attempted.
Sensorium: clear.
Orientation: good.
Amnesia for certain events, following recovery.

CASE REPORT: A. B., thirty-two years of age, was a mechanic by trade, married, but childless. He was a chronic alcoholic and frequently absented himself from home. On one occasion he met a certain man with whom he began sharing a room. One day A. B. commenced to pull down the shades. When his companion asked him why, he answered nervously that he was being watched, that people were calling him vile names and were accusing him of homosexual practices. Voices were asking: "Why don't you kill yourself?" His companion tried to reason with him. He would not listen but ran upstairs to the roof, intending to jump off. His companion caught up with him just in time. A little later he went for a walk, during which the voices continued to threaten: "If you don't kill yourself, we'll kill you!" Coming to a liquor store, he dove head-first through the plate glass window and sustained a severe gash in his scalp. He was taken to Harlem Hospital, where he showed great fear and had to be watched closely. He tried to squeeze his head between the bars of his bed. A policeman attempted to stop him. He grabbed the policeman's gun, shot and killed him.

A week later, the hallucinations and delusions disappeared. There was complete amnesia for the period.

Chronic Hallucinatory Psychosis.—The manifestations are like those of acute alcoholic hallucinosis, but instead of lasting for a brief period of several days to a month, the patient continues to be psychotic until deterioration sets in.

Chronic Alcoholic Paranoid:

The delusions become fixed.
Deterioration is progressive.
The patient becomes:
Irritable, abusive and readily angered; *or*
Jolly, flippant and careless of personal appearance.
He may believe that he is great in his field of endeavor; *or*
He may be moody and cry readily.
Ability lessens.
The power to keep the goal in mind diminishes.
Inattention supplants interest.
Falsification and unreliability take the place of truthfulness and integrity.
Suspicions displace confidence.
Delusional trends of infidelity develop and the patient becomes unbearable to his family.

CASE REPORT: B. C. was forty-two years old, a builder, married, childless. Although a member of a fine family, he was always a heavy drinker. He began to neglect his family, staying away for days at a time. He would brag that he could build houses as well as any man, but on several occasions was sued for producing unsatisfactory work. Formerly a good mixer, he began to shun all social functions. He became markedly irritable and suspicious. He asked his wife on several occasions if she had had other men. His appearance deteriorated. Instead of neat he was slovenly. He became so inattentive that several times he was almost run down by an automobile while crossing a street. He became impotent. His disorientation progressed, and commitment to a state hospital became inevitable.

PSYCHOSES DUE TO DRUGS

Although the general practitioner rarely meets with psychosis due to drugs, nevertheless it is desirable that he have some knowledge of this type of toxic psychosis. Without it, he may fail to recognize the basic cause of the complaints of patients who happen to be addicts. For example, a patient may consult the doctor complaining of cough, pain in the chest, expectoration streaked with blood, loss of weight and weakness. Examination may disclose pulmonary tuberculosis. Without going into the matter further, the doctor may then prescribe medication, possibly including an opiate, and advise the patient as to further treatment.

When the patient telephones the next day to say, "I'm all out of medicine, Doctor," he is surprised.

"That medicine," he answers, "should have lasted you three days."

"Well, I had such a bad night that I took it more frequently

than you directed. Won't you renew my prescription?" (He may say he dropped the bottle and it broke.)

The doctor writes another prescription, gives it to the patient and never sees him again. Another doctor is consulted. The addict goes to first one doctor and then to another.

Scrutiny of the arms and thighs for telltale bluish marks, or running his fingers over the skin of the patient's arms and thighs for little lumps or scars like vaccination marks, representing *sites of hypodermic injections,* would have enabled the physician to discover the addiction.

Most addicts suffer from *bronchitis;* a great many have *tuberculosis.* At first the drug acts as a sedative, decreasing bronchial secretion. Later, the effect is to irritate the bronchial mucous membrane. This irritation, plus loss of appetite and constipation, leads to a toxic state which, intensified by the individual's irregular mode of living, predisposes to tuberculosis.

While taking the drug in quantity which is not excessive but is sufficient to prevent withdrawal symptoms the addict may behave as any other person. If he does not receive a sufficient amount he may develop these *withdrawal symptoms.* The suffering at such time is really intense. Yawning, sneezing, hallucinations, abdominal pains, vomiting, diarrhea, pains of a darting character in the legs, apprehension and suicidal tendencies occur during this period. The idea that an addict takes the drug to give him the feeling that he is sitting atop of the world is false. Once a person is addicted he takes the drug to prevent the suffering of withdrawal.

The textbook concept of *pinpoint pupils* is not always true. The average addict presents pinpoint pupils only when he has taken a dose much too great for his needs. This does not imply poisoning, although it necessarily follows that if a sufficiently large dose is taken by the addict to cause poisoning the pupils will be pinpoint.

The *respiratory rate* is decreased in all addicts. In poisoning it may be slowed down to four a minute.

Endocrine disturbance is manifested in many women addicts by cessation of menstruation and by temporary sterility in men.

Personal experience with many thousands of addicts, dur-

ing the years in which I was Chief Physician of the Tombs Prison, and since that time, has led me to the conclusion that fully 50 per cent of the habitual users of narcotics had a *psychopathic personality* prior to their addiction. Those who were stable previous to addiction develop a change in personality resembling psychopathic personality, with continued use of the drug.

Psychopathic personality, as I shall state again later, implies a deviation from the normal characterized by defective volition, poor judgment, impaired reasoning power, and marked emotional instability. Those possessing such a personality are inaccessible, believe they know better than anyone else what they are doing, and seldom, if ever, profit by experience.

Psychosis due to Morphine Addiction.—The habitual morphine user is a rather bitter person. Although he tries to give the impression that he does not care what the world thinks of him, he does. Many suicidal attempts are born of the addict's realization that he is a social outcast, looked upon with disdain by the public. He becomes selfish and is concerned only with himself. He lives in a narrow world where criticism, authority and advice are resented. He associates with other addicts, shunning society in general. Not all addicts, however, neglect business. Many professional people, for example song writers, are addicted to morphine because it gives them a sense of security and they believe that it enhances the quality of their work.

Large quantities of morphine taken daily for many years will result in mental deterioration and, in some instances, in a definite psychosis. The outstanding features of such a psychosis are:

Delusions of persecution.
Delusions of infidelity.
Intense jealousy.
Impairment of memory.
Disturbance in the power to concentrate.
Episodes of depression with ideas of self-destruction.

Psychosis due to Heroin Addiction.—Heroin, a derivative of morphine but more powerful, is the drug favored by the underworld addict. The effect upon the personality is

more pronounced than is that of morphine: disintegration is quickly evident. The heroin user is more apt to commit an overt act than is the morphine addict.

CASE REPORT: E. F. was thirty-two years of age, and an actor by profession. He was married but childless. He had been addicted to morphine for five years, and to heroin for seven years.

When I examined him his basic personality revealed marked instability. During the last few years of his morphine addiction he had been unable to find work. He lost interest and became depressed. His wife, who was employed, supported him. To save money he switched from morphine to heroin, which was less costly. He became more discouraged and depressed. Treatments for his addiction were always followed by a return to the drug.

He became surly and seclusive, refusing to visit even his friends. He accused his wife of going out with other men, and, in particular, of being in love with a man in the office where she worked. He couldn't sleep. If his wife tried to reason with him, he became resentful. He grew very jealous and began to follow her in order to see whom she met and on several occasions was assaultive. He developed the delusion that he was being watched and followed by the police. It finally became necessary to commit him to a private sanatorium where he was again taken off the drug. After three months he was discharged as a "recovery." Several months later I again had him as an addict patient.

Psychosis due to Cocaine Addiction.—Psychosis due to addiction to cocaine is much less frequent, except in certain communities, than it was a few years ago, due to the growing popularity of marijuana. In other words, marijuana (Cannabis indica) has, in great measure, taken the place of cocaine.

Effect of the drug before addiction has been firmly established:

There is a feeling of exhilaration.
The stream of thought is facilitated.
Great energy is engendered.
The addict becomes talkative and sometimes very witty.

As addiction develops:

There is a marked interference with moral values.
The addict becomes confused; the sensorium is disturbed.
Irritability and surliness may replace a previously agreeable disposition.
Delusions make their appearance:
Delusions of persecution, often directed against members of the family, are common.
Hallucinations, particularly visual, are frequent and troublesome.
Restlessness brings about what is commonly called "the leaps"; the individual seems to jump around.

The history reveals:

A previously existing psychopathic personality in the majority of cases.
Diminishing appetite.
Loss of weight.
Increasing weakness.
A sensation as of bugs crawling under the skin.

Physical findings:

Emaciation.
Anemia.
Increased pulse rate.
Dilated pupils.
Twitching of various muscle groups, particularly of the face and legs.
In many cases, there is atrophy of the muscles of the hands and legs, with wrist and ankle drop.
Tremors of the hands and tongue are usually present.
Speech may be slurred.
Convulsions may occur.
Drying of the mucous membrane of the nose is present in those who take the drug by sniffing; ulceration or perforation of the nasal septum is not uncommon.
A psychosis may develop. The following history best illustrates this condition:

CASE REPORT: G. H., thirty-three years of age, white, single, without occupation, began using cocaine through evil associations. One day while reading in the subway he took off, first his shoes and socks, then his coat and shirt. He was hunting the bugs that were crawling under his skin. He was oblivious to all else. The conductor compelled him to dress and ejected him at the next stop. By the time he reached the sidewalk he was convinced he was being followed. All the people he passed had evil expressions. He walked faster to escape them; they, too, walked faster. When he ran, they ran. Coming to a house that seemed to offer asylum, he ran up the stairs and burst into a room. When he saw a woman there, he sank to his knees and begged her to protect him against the people who wanted to kill him. The woman's screams aroused the neighbors. They called a policeman and the man was arrested. He was found insane by a Lunacy Commission and committed to Matteawan.

Combined Opiate and Cocaine Addiction.—I have never seen this topic discussed in any book on psychiatry. Taken singly, each drug may lead to psychotic manifestations; combined, the following symptoms appear:

There is a striking disintegration of personality.
Emotional deterioration is rapid and marked.
Moral laxness develops; there is a tendency to pervert practices.
Memory becomes impaired.
The addict becomes careless about his person and habits.
Irritability and episodes of excitement are common.

If the addiction continues and a psychosis develops, we may find the following manifestations:

Delusions of persecution and infidelity appear.
Hallucinations—visual, tactile, and auditory—are frequent.
Fatigue is marked.
The capacity for work is reduced to a minimum, if not lost altogether.

CASE REPORT: I. J., a married salesman, thirty-four years of age, had always been an unstable person and had worked for men engaged in questionable enterprises. After ten years of combined heroin and cocaine addiction, he had to be committed to a state hospital.

Two years before his commitment he became surly, intensely jealous, and accused his wife frequently of infidelity. He tired easily and became slovenly. Auditory and tactile hallucinations were pronounced. He was certain that somebody was "out to get" him, and that he was constantly followed. He became so confused and unable to concentrate that he could not keep a goal in mind. He underwent a course of treatment without avail; his symptoms were worse afterward. He now had dizzy spells and almost constant headache. His delusions of persecution were intensified. His insight and judgment became hopelessly impaired. There was no alternative to his commitment.

Marijuana.—The use of Cannabis indica has increased alarmingly in the past twelve years. Young people are more prone to use the drug, which is smoked generally as a cigarette known as a reefer or muggle, than are adults. Some authors have described schizophrenic, manic-depressive, and toxic reactions to marijuana. Those who have made these distinctions, however, have as a rule not had much experience with marijuana users. Actually, the basic personality pattern governs the psychotic manifestations.

Certain features common to all psychoses attributable to marijuana addiction:

Auditory and visual hallucinations.
Delusions of persecution.
Ideas of reference.
Flight of ideas.
Sexual conflicts.
Suicidal attempts, in some cases.

Acute state: In the acute state of marijuana intoxication, the symptoms vary with the basic personality of the individual.

Some people are flighty, talkative and inclined to sing and carry on as under the influence of alcohol.
They may be agitated and profane

If sexually excited by the drug, there are visual hallucinations of a sex character and sexual assaults may be committed.
Insomnia may be present, but is not the rule.
Other individuals become apprehensive, agitated and/or depressed.
They experience a ringing in the ears and dizziness.
They have the feeling of walking on air.
Appreciation of the time-relationship disappears.
Suicide may be attempted.

The intensity of the symptoms depends on:

1. The type of marijuana used. That grown in the north is much less potent than marijuana grown in the southern part of the United States or in South America.

2. Smoking on an empty or full stomach. The effect is more pronounced if the drug is smoked when one is hungry.

3. Smoking indoors or outside. If inside, the manifestations are more rapid and intense than in the open.

CASE REPORT: K. L., a Puerto Rican chauffeur, twenty-four years of age, single, was a marijuana addict for five of the twelve years of his life in the United States. He had not had steady employment for four years. On the few occasions when he succeeded in obtaining work as a chauffeur he was unable to keep the position because of inability to concentrate and being in a "fog." He thought no one cared for him and that people were singing songs with reference to him. He found it impossible to sleep because of threats in the air that he would not be allowed to go home; when he was home, he became noisy, excitable and was frequently incoherent. If he succeeded in falling asleep, his legs would begin to jerk and he would wake up. He would then get out of bed and walk around the house, regardless of any women visitors who might be there.

When I examined K. L., he told me that the neighbors looked at him in a peculiar way and that people were calling him a pimp and a gigolo, making "wise cracks" at his expense. His emotional reactions were entirely inappropriate. He was found insane and committed to Matteawan.

For the past several years this man had smoked ten marijuana cigarettes a day and in addition had soaked marijuana cigarettes in water and had then drunk the water.

INVOLUTION MELANCHOLIA

This condition is seen most often in women between the ages of forty-five and fifty, and in men from fifty to sixty years of age. These are the periods of endocrine change. Those who develop melancholia are generally of a rather worrisome type, not given much to social life, "home bodies" satisfied to go along, working hard and playing little. The woman begins to feel that she is no longer as desirable or acceptable to her husband as formerly.

Both men and women tire readily. Their energy and strength are waning and they may become convinced they have not long to live. The man begins to realize how little he has accomplished and may find, to his dismay, that he is no longer potent. If, at this point, some misfortune occurs, like the loss of position due to age, or due to the commission of some overt act, or due to failure in business so that idleness replaces activity, the stage is set for the appearance of pronounced psychotic symptoms.

The individual is now convinced that he or she is no longer of any use to the family and that the misfortune is punishment for past sins. Death would be an atonement. He is unworthy; there is nothing left to live for. He is greatly agitated and distressed. Hallucinations and confusion may occur. As a rule, orientation is unimpaired. He loses all interest in his environment and develops great fear.

The appetite diminishes and there is loss of weight. Cyanosis and coldness of the extremities are common symptoms. Constipation is the rule and insomnia may be marked. Ideas that their "insides are washing away," or that their intestines are "knotted" and "rotting" are common. These symptoms and the attendant depression and delusions make these the most miserable of all human beings. It is necessary to watch them carefully to guard against suicide.

CASE REPORT: Mrs. M. N., fifty-one years of age, married and the mother of one child, was a quiet, well-educated refined little woman who attended to her home duties meticulously. She was always religious and had many friends who came to see her and whom she visited often. For several years she had suffered from pain in the back due to a pronounced uterine prolapse At forty-eight her menstrual periods ceased. A year later she began to have frequent attacks of neuritis. Her blood pressure mounted and she complained of pain and a "feeling of pressure" in the head. But she had no psychosis.

Then her son became involved in a fraudulent transaction and was arrested, causing her great worry and shame. This was the "last straw." She became markedly depressed, suffered from insomnia, lost her appetite and lost weight. She began to accuse herself of a terrible "sin" and insisted that her son's predicament was due to this. She would pace the floor, wring her hands and bite her forearm, crying: "Why did I do it?" She would ask this over and over. Her continual lament was, "I should die! I am of no use to my family! There is no hope!" When friends visited her, she would ask, "Why do you come to see me? I am so unworthy!"

She became emaciated. The skin of her face grew lined and her body stooped. Her hands were always cold. Now she was very quiet and would sit in her chair, markedly depressed and saying little, for hours at a time. If

questioned, she would answer briefly. She stated that her bowels could not move because her intestines were in knots and she was rotting inside.

Treatment at a private sanatorium was deemed advisable. At the end of two years, her condition had so improved that she was released on parole to her husband.

ANTEPARTUM AND PUERPERAL MENTAL DISORDERS

Antepartum.—The general practitioner and the obstetrician, in particular, frequently encounter mental disorders associated with pregnancy and childbirth. The disorders encountered during pregnancy are not necessarily classified as psychoses. They are, however, of psychiatric interest.

There are some women who dread pregnancy. Such an individual has in mind a history of insanity or marked nervous disease in her immediate family or in her husband's family. She believes, therefore, that the child may some day become insane or develop a nervous disorder. It is strange how often this apprehension is seen in the more intelligent women.

Other women fear the ordeal of pregnancy and, in particular, of labor. In these women the entire disposition seems to change. They become irritable, worry about whether or not they will be able to have the baby and dread the coming delivery. Many women belonging to this group take emmenagogues and try every measure to bring about an abortion in the early stage of pregnancy. A high percentage are determined not to have the child and finally visit the abortionist who is more than eager to help them. Should the woman, after trying various remedies, finally decide to have a child she may worry that the child will be disfigured or prove to be an idiot. In these cases, there may be marked depression and emotional disturbance may be a prominent feature. We must at all times in these cases remember the *basic personality* of the woman. In neurotic and hysterical patients, pregnancy may serve to accentuate defects in personality.

Strange *desires* and *impulses* may occur during pregnancy. There is a superstition among certain people that every desire of a pregnant woman should be satisfied else it may result in the birth of an abnormal child. There are women who have been total abstainers who suddenly develop an overwhelming desire for beer. Illustrations of this nature may be cited with

ease by most obstetricians. There are, however, women who develop a morbid impulse to take things. A famous case illustrating this acquisitive propensity involved a certain Mrs. Y., who had been arrested several times and was to be tried as a fourth offender. Conviction would have meant life imprisonment. It was proved that on each occasion, when arrested, she was pregnant. This case received much publicity at the time. Many psychiatrists throughout the country were asked to give their opinion. The woman, as a result, was not convicted as a fourth offender and received proper consideration from the court.

Puerperal.—The puerperium may precipitate a psychosis by reducing the patient's energy and thus, acting upon an unstable personality organization, bring about a mental disorder. In this condition one should remember that there really is no such definite disease as puerperal psychosis. The disorder that does occur may take one of several forms such as, in order of frequency, *manic-depressive, schizophrenic,* psychosis with *psychopathic personality* and *toxic-exhaustive states.* Certain psychiatrists place little stress on the *toxic element* in the production of postpartum mental disorders. It does, however, seem that in certain cases the indications point to a toxic state and quite logically to a mental disorder brought about by such state. In the consideration of other etiologic factors it has been found that Jewish women most frequently are affected, that in many cases of the disturbance there is a history of prolonged courtship, that such women often have homosexual tendencies, that any number of such women become hypersexed following delivery and then become frigid. As regards the last statement there are certain investigators who have found that the reverse is true. In all cases, however, what is most important is a study of the *basic personality.* This is the soil which makes possible and probable the development of the mental disorder.

In the *manic-depressive type* the patient may present manifestations referable to the child, she may refuse to acknowledge that the baby is hers, refuse to nurse the baby, and absolutely ignore it. Some women give the child away. Others are constantly in dread that the baby will die. The woman may say that her baby is dead. She may try to injure the child. In one

of my court cases, while the nurse was out of the room, the mother picked up the child, walked to the window, dropped the child out of the window, and then went back to bed.

The woman may be distinctly hostile to her husband, may say that he is not her husband or may accuse him of infidelity.

There may be confusion and some clouding of consciousness. Insight is faulty. The mental trend may shift.

There are certain cases in which the patient presents extreme emotional swings. She may be excited and apprehensive. It may be difficult to keep her in bed. Speech may be incoherent. In the intensely agitated, orientation may be faulty.

CASE REPORT: O. P. was a young woman in her late twenties. While pregnant she went for an automobile ride. When the car slowed down she got out before it stopped and fell heavily, sustaining bruises. The next morning she gave birth to her baby and several days later began to manifest psychotic symptoms. She complained that the infant was not hers and refused to nurse it. Her antagonism towards her husband was pronounced. She was so restless that it was difficult to keep her in bed. Her speech was incoherent at times and orientation was disturbed. Her insight was also poor.

After several months in a state hospital she was discharged as cured.

The patient's pre-psychotic history indicated that she was a worrisome type, but there was no history of marked depression or abnormal emotional display.

Two years later, the woman again gave birth to a child. There was no history of an accident but she had a recurrence of the psychotic manifestations. Actually, she suffered from manic-depressive psychosis, the mental disorder being precipitated by childbirth.

There are other cases who are depressed. Negativism may be present. In most cases sleep is disturbed. Physically one notes loss of appetite and impairment in strength. Constipation may be present.

The symptoms of *schizophrenic* puerperal disorders vary little from those found in the nonpuerperal form of this mental disturbance. True, in many instances the delusional content may have reference to the baby. The mother may believe that she is unworthy of having the baby or she may believe that her baby is to be destroyed. There may be certain manic features in this schizophrenia. Among these are antagonism towards the husband and an attempt on the part of the patient to injure or destroy the child.

With regard to the *toxic-exhaustive type,* one sometimes

finds cases of toxemia following childbirth in which the patient presents distinct evidence of mental disturbance. Delirious manifestations may occur, with clouding of the consciousness, great restlessness, disturbance of orientation, amnesia, loss of insight and, in certain instances, dementia. In addition, there is an accentuation of personality defects. The outstanding physical symptoms are fever, loss of appetite, loss of weight and exhaustion.

EPILEPTIC PSYCHOSES

Although epilepsy itself does not denote a psychosis, it may lead to definite mental disorder. The usual classification of epilepsy is symptomatic, idiopathic and Jacksonian. White and Jelliffe, however, have suggested grouping the episodes as (1) those caused by gross brain disease, (2) those originating in a toxic or infectious condition, and (3) anomalies and borderline conditions. I shall not discuss epilepsy proper, but shall confine myself to manifestations of psychiatric significance.

There are psychiatrists who deny the *epileptic personality* and attribute all personality changes directly to the epilepsy. I have found that certain personality characteristics are present in nearly all epileptics. These individuals are usually emotionally unstable, egoistic, religiously inclined, and very impulsive even to the degree of being violently explosive. They are resentful of authority and distrustful. Many have indefinite complaints. Others are moody and keep to themselves. Occasionally, their acts are sadistic in nature. Irritability and bad temper may make it difficult to associate or deal with the epileptic. In addition to these general manifestations, there are others which may characterize the different epileptic states.

Considering epilepsy, per se, we may find the following:

Aura:

During the aura, which lasts only a few seconds, there may be hallucinations:
- Auditory.
- Visual, with streaks of lightning, flashes of light and terrifying animals.

Symptomatically, there may be a feeling of constriction in the chest, throat or head.
A sensation of heat or cold is experienced.
There may be shooting pains in the arm or leg.
There may be profuse perspiration.
The individual may suddenly start to run.

Epileptic Equivalent:

During this period, which may be short or last for several weeks, convulsive attacks are absent, the equivalent state taking the place of the convulsive seizure.

Actions are usually carried out automatically and they may have the appearance of deliberate acts.

Failure to recognize acquaintances may be marked.

It is not unusual for the patient, at the beginning of the equivalent state, to continue whatever act he was carrying out when the seizure occurred.

Example: A woman who was cutting bread when the attack began, continued the cutting operation and cut off her child's arm.

Amnesia for the period of equivalence is the rule, a fact of tremendous medicolegal importance.

Epileptic Furor.—When a person has suffered from epilepsy for several years, a state of epileptic furor, marked by extreme excitement, may occur. In one case, the patient was so violently assaultive during the epileptic furor that he had to be committed to an observation pavilion. He was eventually adjudged insane and committed to a state hospital.

Post-epileptic State.—Following the convulsive seizure, there is usually a period of confusion—a *dream state*. Occasionally there is maniacal delirium. As with the epileptic equivalent, an act begun before the seizure may be continued.

CASE REPORT: Q. R., a janitor, had been an epileptic for many years. He went to a saloon where he had several drinks. When he paid for these the bartender short-changed him. In the course of the argument that followed, Q. R. pulled a knife and threatened to cut the bartender's throat. He was finally expelled from the saloon, muttering and confused. On arriving home he attacked his wife and cut her throat so that she bled to death. He had absolutely no recollection of the act.

GENERAL PARESIS

(General Paralysis or Dementia Paralytica)

Occasionally one meets with juvenile paresis, occurring before the twentieth year. However, the disease usually appears in males between forty and fifty years of age, and generally develops from ten to twenty years following infection with syphilis. As a rule there has been little or no treatment during the early stage of the disease. Various precipitating factors for paresis may be mentioned. Among these are an accident, such as a head injury, alcoholic excess, and great stress and strain.

Cerebrospinal fluid findings:

Normally, the number of cells in a cubic millimeter of spinal fluid is from 1 to 4 or 5. When the number exceeds 10 and there is evidence of a psychosis, paresis should be suspected.

The normal pressure of the cerebrospinal fluid is from 90 to 160 mm. of water with the patient in a recumbent position. In paresis the pressure may be substantially increased.

The Wassermann reaction of the fluid is usually strongly positive in paresis.

The protein content of the fluid is increased and globulin may be present in considerable amount.

There is a distinctive colloidal gold reaction and a paretic curve.

Neurologic findings:

The pupils may show difference in size, may be irregular and there may be evidence of atrophy of the optic nerve.

There may be loss of pupillary reflex to light (Argyll Robertson pupil).

The Romberg test is positive, namely, there is marked swaying of the body when the feet are closely approximated, in a standing position, with the eyes closed.

The gait may be shuffling.

Tremors of the outstretched hands and of the tongue are common.

Twitching about the mouth and face may occur.

The tendon reflexes may be increased.

Symptomatically:

The onset is usually insidious.

There is a change in personality.

The patient becomes restless and may show marked mood alteration, *or* he may become listless and refuse to mingle freely, preferring to be alone.

Depression is not uncommon.

Memory may be impaired.

Insight and judgment may be defective.

There may be intellectual impairment and changes in the moral sphere.

Speech defect, particularly slurring, may be present early in the disease. The patient is best tested for this by asking him to repeat certain sentences, such as:

"Round the rugged rock the ragged rascal ran."

"Liquid linoleum."

"Methodist Episcopal."

Later, the patient may become euphoric.

He may have delusions of grandeur.

He may present symptoms common to certain classifications of this disease (expansive, depressive or deteriorating type).

He may lose weight, be constipated and suffer from disturbance of vision.

In the terminal stage, there may be a complete disruption of the mental processes.

Expansive Type:

There are delusions of grandeur.
Euphoria.
Thickened speech.
Defective memory.
There are periods of irritability and excitement.
There are typical neurologic and serologic findings, illustrated in the following case report:

CASE REPORT: S. T. was forty-two years old, married, and a painter. His wife had had two premature births. Twelve years before I examined S. T. he had had a chancre. The "sore" disappeared following the application of an ointment recommended by a druggist. Ten years later his personality began to change. He said he was tired of working as a painter. He had so much *money* he did not need to work! He began to dress in style. Obtaining a check book, he wrote a check for $100,000 and gave it to his wife. He wrote many other checks—none for less than $100,000. He was soon arrested for forgery. In the Tombs Prison he claimed to own a great deal of property, to be a millionaire, and to have a cellar well stocked with the finest wines.

Examination revealed a grandiose delusional content. Memory was defective, there was disorientation for time and place, general information was poor, judgment and reasoning were impaired, and the speech was so slurred that he failed in all test sentences. Insomnia was marked.

The *neurologic findings* were: typical Argyll Robertson pupils, a positive Romberg, absent patellar and Achilles reflexes. The *laboratory findings* were: Wassermann 4 plus in both the blood and spinal fluid. There was a typical colloidal gold reaction and paretic curve.

It was necessary to commit the patient to Matteawan.

Depressive Type.—A typical case will convey the picture of the depressive type of paresis very well.

CASE REPORT: U. V. was a married, childless salesman, forty-one years of age. His history of syphilis dated back fifteen years. He had always been a neat dresser and excellent at his work. Then he began to lose his "pep" and initiative. He became slovenly, complained of headache, was markedly depressed and wept often. He gave up his work and did not wish to leave the house. When he did go out, he would pick up cigarette butts from the gutter. Indoors, he would walk about, bewildered, picking things off the floor. Insomnia was marked.

Examination revealed poor insight and judgment, fair orientation, coherent but unproductive talk, no definite delusional or hallucinatory content, no speech defect on test sentences, and fair general information.

The *neurologic* and *laboratory findings* were: pupils fixed to light, a positive Romberg, exaggerated patellar reflexes, 4 plus cerebrospinal fluid Wassermann, and a colloidal gold reaction typical for paresis.

This man was found insane and committed to Matteawan.

Deteriorating Type.—As the psychiatrist to the District Attorney of the County of New York I was asked recently to

represent the office at an examination of a man who proved to have a typical deteriorating type of general paresis. The mental examination was conducted at Bellevue Hospital, where W. Y. was a patient. He had been accused of felonious assault. From an acquaintance of W. Y., I learned that he was fifty years of age, a native of Russia and a resident of the United States for twenty years. There was a history of syphilitic invasion for about fifteen years. There was also a history of excessive alcoholic indulgence for about five years. It was impossible to obtain any other information. Some of the questions and answers were the following:

Q. "How do you feel?"
A. "Red Russians. It is America. Yes, Russia. Ten thousand dollars."
Q. "How long have you been here?"
A. "Bolsheviks all kill—Why? I am a Communist."
Q. "What day of the week is it?"
A. "It cannot happen. The Revolution. Everybody killed. Ten thousand dollars."

The man was greatly agitated, mumbled incoherently and none of his answers was relevant.

The cerebrospinal fluid indicated 4 plus Wassermann and there was found a typical paretic curve. Lack of cooperation due to deterioration made it impossible to perform a neurologic examination. I did know, however, that his pupils were irregular and that the light reflex was absent.

In other cases of a similar nature, I have found absence of patellar reflexes, Argyll Robertson pupils, and a positive Romberg. In cases of deterioration not as marked as the case cited, where cooperation is possible, a test of the handwriting sometimes reveals mistakes in spelling and tremor of the hands.

PSYCHOPATHIC PERSONALITY

Psychopathic personality does not in and of itself imply a psychosis. It does, however, signify a deviation from the normal, and embraces a group of humans who do not belong in state hospitals as they are constituted at present, but who do present certain instabilities and abnormal traits. Present since early life, these traits stamp the individual as peculiar, to say

the least. He is inaccessible, emotionally unstable, and unable to profit by experience because of defect in judgment. He may later present sexual pervert activity and behavior bordering on or actually criminal. Of this type of individual the Department of Mental Hygiene of the State of New York states: "The type of behavior disorder, the social reactions, the trends of interest, et cetera, which psychopathic personalities may show, give special features to many cases, *e.g.*, criminal traits, moral deficiency, tramp life, sexual perversions and various temperamental peculiarities." (Hinsie: "Syllabus of Psychiatry.")

It is to be remembered that a true psychosis may develop atop of a psychopathic personality. Women belonging to this group readily become prostitutes, drug addicts, chronic alcoholics and criminals. This does not, however, imply that every drug addict, every chronic alcoholic and every habitual offender belongs to this group. We are too prone to append psychopathic personality to our diagnosis in both psychiatric practice and in the consideration of criminals. Psychopathic personality, per se, is no defense in a criminal action nor is it sufficient, in certain civil actions, to label the person as irresponsible. If this were so, fully 33 per cent of our criminals would be acquitted and the trial of issues in the Surrogate's Courts would be greatly complicated. Nevertheless, these individuals are deviated from the normal. For many years I have asked that an intermediary institution be created for the study and treatment of these people. They do not belong in insane asylums nor do they profit by incarceration in prison. However, until such institutions are created, the psychopathic personalities who do commit crimes must be sent to penal institutions.

SUMMARY AND CONCLUSIONS

I wish to stress the fact that this paper is intended solely as an aid to the general practitioner and to the specialist who is not a psychiatrist. I have not dwelt on pathology, nor have I given details of treatment. I have avoided state hospital English as much as possible. It has been impossible, obviously, to cover the entire field of mental disease. I have outlined, however, certain mental diseases most likely to be met with in patients visiting the doctor's office. These are schizophrenia

(dementia praecox), manic-depressive psychosis, alcoholic psychoses, epilepsy and narcotic addiction disturbances. In addition I have discussed involution melancholia, antepartum and puerperal mental disorders and general paralysis, and have mentioned briefly psychopathic personality. It should be remembered that not every case of psychosis is a typical text-book case.

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CLINIC OF DR. JOSEPH WORTIS

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PHYSIOLOGICAL TREATMENT OF THE PSYCHOSES

Some Recent Developments

SHOCK THERAPY

IT is interesting to compare the number of reports that have appeared in the *Index Medicus* on the subject of dementia praecox therapy before and after the discovery of the insulin shock treatment. Before 1933, at most a few dozen papers on the subject would appear each year throughout the world; since then so many hundreds of reports have been coming out that the reading of the literature on shock treatment alone almost constitutes a vocation. Moreover, a whole series of developments in psychiatric therapy has come in its wake. For a number of reasons it seems best to call these new developments in treatment physiological, because their common characteristic is the deliberate production of physiological changes for therapeutic effect on psychiatric disorders. They contrast sharply with the psychological treatments which until recently were used so widely and almost exclusively over the whole range of psychiatric disorders.

It would be a mistake to suppose that coma, or the suspension of brain metabolism, is the crucial factor in these new treatments. Before the development of the insulin shock treatment, Sakel successfully used nonshock doses in the treatment of morphinism, as Klemperer had used them in the treatment of alcoholism before him. Insulin had proved helpful in the hands of many earlier workers[1] even when given in combination with glucose, without the development of hypoglycemia, and it is

already well established that hypoglycemia is not always essential for the efficacy of insulin therapy—in fact, recent work by Hammargren and Stenberg[2] has thrown considerable doubt on the advisability of inducing coma routinely in the course of treatment.

The *metrazol treatment* is also experiencing a similar diffusion of theory and method. Meduna claimed no specific value for metrazol: from the beginning he preferred to call his method simply "convulsant," leaving the door open for other drugs—triazol,[3, 4] camphor,[5] and picrotoxin[6]—that might do as well or better. But it would appear that subconvulsive doses are also frequently effective; reports published in France last year from several sources[7] claim excellent results with nonconvulsant doses of metrazol administered by slow intravenous injection. And in the treatment of alcoholism a number of nonconvulsive stimulants, including lobeline, strychnine and benzedrine, have been employed to advantage.

Some of the recent physiological treatments do not make use of drugs at all. An *anoxic treatment* has been developed by Himwich and Alexander,[8, 9] for example, involving the temporary displacement of oxygen by nitrogen in the inspired air. There also has been a revival of interest in the use of *faradic electrical stimulation*[10] in psychiatric treatment, and convulsions can be very conveniently induced in this way. Although I cannot do much more in this short space than indicate a trend, I shall try to discuss briefly some of the more important of these newer developments in the physiological treatment of the psychoses.

Variations in the Technic of Insulin Shock Treatment.—*Attempts to Make Treatment More Intensive.*—The dramatic psychiatric improvement that followed unintentionally prolonged coma in certain cases suggested to more than one observer that, if a safe method for prolongation of coma could be devised, it might further extend the value of insulin shock treatment. Kraulis[11] therefore proposed the administration of small amounts of *sugar* by stomach tube at intervals during insulin shock to keep the patient in coma, with a blood sugar level sustained between 40 and 60 mg. per cent (determined by the method of Hagedorn-Jensen) to insure prompt reversi-

bility. The presence of pyloric spasm in many cases of prolonged coma[12] would seem to me to make intravenous administration of sugar essential in any such therapeutic undertaking, although it still remains a precarious procedure at best and is not yet suitable for general clinical application.

There have, however, been other methods proposed for intensifying the shock effect. These involve the production of convulsions in coma by *metrazol* or *electric stimulation* (which we shall soon discuss), or the intensification of the coma by the superimposition of *nitrogen inhalation*.[13] Though the method of inducing seizures during hypoglycemia has much to recommend it, the advisability of the more drastic procedures seems to me to be too questionable to be worth the risks they now entail.

Attempts to Make Treatment Less Intensive.—It is curious to consider that at this late date so little has been done systematically to evaluate the therapeutic effects of large doses of insulin, without the development of coma, in cases of schizophrenia. Before the era of large insulin doses, the value of *glucose-insulin treatment* had been amply confirmed in a variety of conditions, including alcoholic psychoses,[14] depressions, certain senile psychoses,[15] neurasthenic conditions and schizophrenia, and in more recent years workers in the field of insulin shock treatment have often reported responses to treatment without the development of a single shock. There has, however, been a general assumption that the therapeutic results of glucose-insulin treatment in schizophrenia cannot compare with those achieved with the orthodox shock treatments. Practically all of the glucose-insulin treatments so far reported in the literature have, however, involved the use of moderate doses of insulin, and it remains to be seen what wider experimentation on the therapeutic effect of 200 units or more of insulin a day, combined with glucose, would reveal. Meanwhile there are frequent occasions when considerations of age, of complicating illness, or of other circumstances make a less elaborate or drastic therapeutic procedure desirable, and I have found the method of combining insulin with glucose a particularly valuable auxiliary to treatment in certain cases of *depression*.

Technic of Glucose-Insulin Therapy.—The procedure is to administer 20 to 60 units of insulin daily in the morning hours, preferably fasting, followed with 50 to 100 gm. of glucose in solution, given by mouth in about an hour, before any marked hypoglycemic symptoms develop. A regular meal is then served within the next half hour. Because of the high carbohydrate consumption involved in all insulin treatments, and because dietary deficiencies are not uncommon in depressions, I have also found it helpful to prescribe 6 to 10 brewers' yeast tablets daily during the course of treatment. In some cases I have also found that higher doses of vitamin B complex, in the form of thiamin, riboflavin and nicotinic acid, are well worth a trial. The glucose-insulin procedure is repeated daily or several times a week over a period of five or six weeks, and has proved very helpful in a considerable number of cases.

The Nitrogen Treatment.—Since both the convulsant and the insulin shock treatments had one common element—the suspension of brain metabolism—the next logical step was to produce this suspension by the simplest possible means. With this in mind Himwich and Alexander devised a simple *anoxic* treatment of schizophrenia, involving the temporary displacement of respiratory oxygen by nitrogen, applied through a mask, until the point of coma is reached. Carbon dioxide is absorbed by soda lime and the patient experiences no subjective distress. Recovery is prompt and the entire procedure takes but a few minutes.

My own personal experience with this type of treatment is limited to a small number of cases treated over a period of weeks, but a valuable discussion of the topic has already appeared,[16] and a full report of the series of twenty-four cases treated at Bellevue Psychiatric Hospital has recently been made by Green and Adriani.[17] The practical value of this treatment is open to question. Several cases in the Bellevue series that proved unresponsive to the nitrogen treatment responded favorably to insulin therapy, so that the anoxic treatment seems to do less for some individuals than the insulin shock procedure. It is possible though that the technic we employed was not altogether the same as the one practiced at Albany. The results of more complete investigations will be awaited with interest, for they will show in the form of a

crucial experiment whether anoxia is the essential factor in these very helpful new treatments.

The Electro-shock Treatment.—As early as 1932[18, 19] it had been noted that electric shock could induce sudden improvement in a schizophrenic psychosis, but it remained for Cerletti and Bini[20] to develop the phenomenon to a therapeutic principle. Faradic stimulation is now the method of choice for

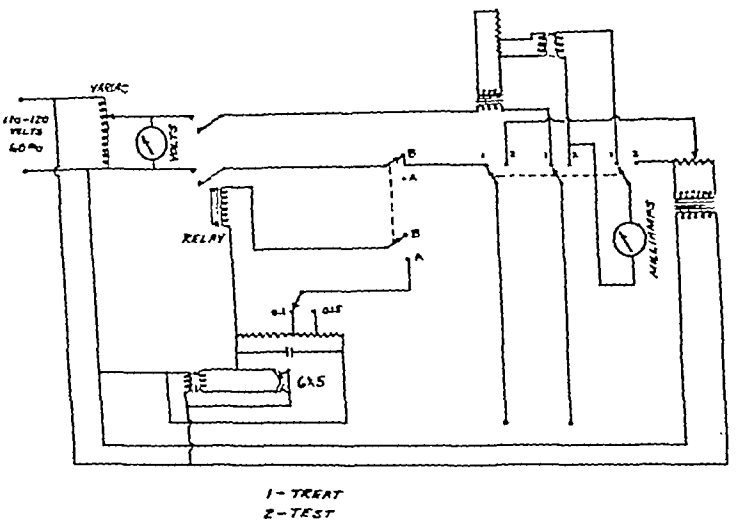

Fig. 60.—The Rahm electro-shock apparatus. An ordinary 110-volt, 60-cycle house current is transformed to the desired voltage through a variable autotransformer. The resistance of the head is measured in advance with an ohmmeter and the voltage adjusted accordingly to secure the desired milliamperage (usually less than 500 m. a.). The timer employed is the delay release relay type, adjustable to 0.1 and 0.15 seconds. The actual milliamperage during the treatment is usually somewhat higher than the calculations according to Ohm's law would lead one to expect, and the resistance between the head electrodes is usually found to be diminished if checked again after treatment.

inducing convulsions.[21, 22] The actual machinery employed is extremely simple, its manipulation is easily learned, and its dangers are relatively slight. The apparatus is contained in a small portable case which may be connected to any ordinary 110 volt 60 cycle A.C. current outlet. The electrodes are applied firmly over the temples with a clamp, the electrical resistance of the head read from an ohmmeter and the voltage

for the shock dose adjusted accordingly by means of a rheostat. The timing is electrically controlled at 0.10 or 0.15 second by a delay release relay. The shock is then induced by the throw of a switch and, if the proper voltage is chosen, a convulsion immediately ensues. If no convulsion results a harmless *absence* occurs. Convulsions are induced daily or several times a week for several weeks, just as with the metrazol convulsive treatment.

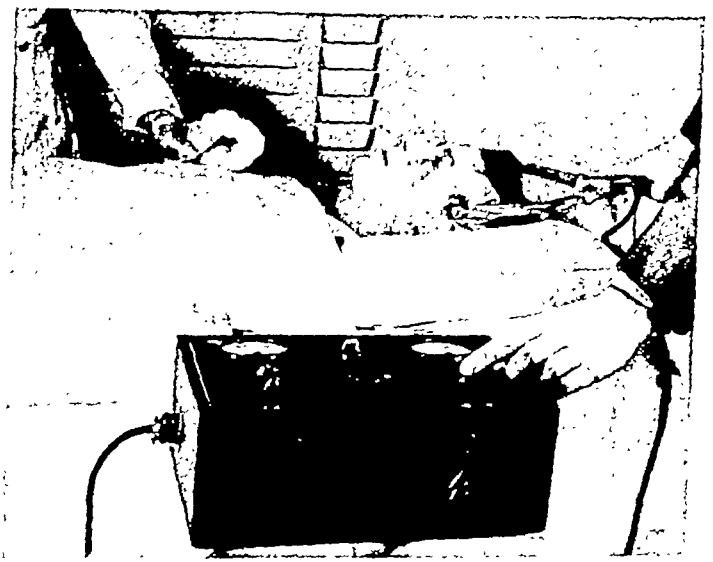

Fig. 61.—Position of the head electrodes in the electro-shock treatment. Hyperextension of the spine minimizes the danger of vertebral compression. A mouth gag is employed during the convulsion.

Convulsions Versus Insulin Coma in the Treatment of Psychoses.—Now that the relative simplicity and economy of the convulsive treatment with metrazol has been even further enhanced by the development of the electro-shock technic, the convulsive treatment has become almost too attractively simple and economical, especially in the treatment of large groups of patients. Its therapeutic efficacy and the permanence of the results, however, seem to me to compare unfavorably with those of the insulin treatment. Though the electro-shock treatment almost eliminates the distressing aura of the metrazol seizure,

the liability to serious fracture and to dislocation still remains, and a substantial proportion of patients subjected to electro-shock treatment suffer vertebral compression. The intensity of the seizure may be diminished, however, by premedication with *curare**[23] or *erythroidin*,[24] by the use of special positions,[25] or by diminution of the voltage, but it is not yet clear whether its therapeutic value is thereby diminished. On the whole, the convulsive treatment still appears to me to be too drastic for routine use, and should be saved for the special indications discussed in a previous clinic.[26]

Brain Injury and the Therapeutic Value of Shock Treatments.—There have been a number of studies purporting to show that the shock treatments produce brain injury. Severe convulsions may produce petechial brain hemorrhage or, more rarely, even more extensive vascular damage. It has also been shown that insulin shock that is unduly intense and prolonged, particularly if associated with multiple seizures, will produce ganglion cell destruction. However, most of the experimental work has been done on animals prone to develop multiple insulin seizures, or has been based on autopsy studies of animals killed with insulin. Schmidt[27] has shown that short daily periods of reversible insulin coma produce no significant brain damage. It is probably incorrect to attribute the value of insulin shock to the stultifying effect of brain damage, and most available clinical and pathologic evidence is against it.

Without undertaking here to evaluate precisely the therapeutic efficacy of shock treatment, its relative value in recent and chronic cases, and the liability to relapse in successfully treated cases, it is perhaps sufficient to quote a cautious and conservative observer, Prof. C. Macfie Campbell[28] of the Harvard Medical School, who recently concluded that "on the whole the general consensus is that the treatment is of value." The shock treatment is already well established among the ordinary hospital procedures at the Phipps Psychiatric Clinic of Johns Hopkins. It is my belief that it still constitutes the

* It should be remembered, however, that drugs of the curare group depress respiration, and that the electro-shock, unlike metrazol, does not directly stimulate respiration. Improper dosage of electro-shock may indeed further depress respiration, so that the combination with curare requires particular caution and should be regarded as experimental at the present stage.

best available treatment for schizophrenia, and has wide applicability to other psychoses.

HORMONES AND HORMONE THERAPY

Out of the welter of productive work in the field of endocrinology, little has so far emerged of direct practical applicability to psychiatry. An outstanding contribution has been Gjessing's[20] monumental work on the periodic metabolic changes in recurrent catatonia. He attributed the alternate negative and positive nitrogen balance of his subjects to a thyroid deficiency, and secured a stabilization of the metabolism, together with amelioration of the catatonic symptoms, by the use of *thyroxin*. But his series of cases, though carefully studied over a period of years, remains small and no confirmatory work comparable to his own has yet appeared. Under the circumstances, a judicious use of thyroid or thyroxin in schizophrenic patients with low basal metabolic rate is permissible, and I have previously recommended its use as an auxiliary to insulin treatment in certain cases.[19] A number of contradictory and inconclusive reports on the use of *estrogenic hormone* in psychiatric disorders—particularly menopausal syndromes—have appeared, but its value has not yet been established.

PSYCHOSES AND DIET

Several papers have appeared in recent years emphasizing on the one hand the occurrence of pellagrous skin lesions[30] among psychotic subjects and on the other hand pointing to mental changes accompanying pellagra[31] as well as other vitamin deficiencies. Vitamin therapy and dietary considerations already have an established place in psychiatry. Depressions of all sorts may accompany various subclinical chronic diseases, and the physician must be alert to the possibility of dietary deficiency,[32] particularly in the low income groups, among food faddists and dieting patients, among those with gastrointestinal disease, and among alcoholics.

MENTAL SYMPTOMS AND ORGANIC DISEASE

"Most of the patients a . . . doctor sees," Sir James Mackenzie once said,[33] "are suffering from ailments in which there are no definite physical signs to record, or in which the signs

have no real relationship to ill-health. The symptoms are subjective, they are feelings and sensations; and long experience has taught me that, to make records of any value of feelings and sensations is a difficult business." Mackenzie therefore raised the dictum: "The early stages of disease are, as a rule, insidious, and are indicated mainly by subjective sensations."

The truth of the statement has been strikingly confirmed in a report[84] on the subsequent course of 100 patients at first diagnosed on a university medical service as neurotic. Within an average period of eight months 24 per cent presented definitely confirmable evidence of various types of organic pathology, which proved fatal in 7 per cent of the cases. But not only do the premonitory stages of many diseases mask themselves as depressions or neurotic complaints, but frank organic disease has its psychological symptoms too. Anemia, heart failure, chronic infection, diabetes, and indeed most organic diseases have their psychological concomitants and are in turn influenced by the patients' mental state.

CONCLUSIONS

It would be a mistake to assume, or to act on the assumption, that physiological treatment represents a new and exclusive therapeutic orientation in psychiatry. These recent developments imply no more and no less than a shift of emphasis and interest along the lines of some new discoveries. Psychological exploration has been a fertile and fruitful field of psychiatric research and treatment for over a generation. It still leaves much to be desired. The shock treatments have opened up new therapeutic possibilities, have served to connect psychiatry more solidly with the rest of medicine, and have brought with them a whole flood of new psychiatric methods and ideas.

There is, however, a continuous connection and interpenetration between physiology and psychology (as there is too between psychology and anthropology) and we must resist the temptation to be too rigid or exclusive in our management of psychiatric problems. The attempt, for instance, to treat homosexuality or malingering by metrazol convulsions represents a perhaps extreme but instructive example of the blunderbuss

appropriation of a legitimate new physiological technic for treatment of psychiatric problems that are remote from the level of physiological integration. It would be a pity if the physiological treatments suffered any discredit because of their random wholesale use in neuroses and other psychiatric disorders that require altogether different management.

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TORTICOLLIS OF CENTRAL ORIGIN

SPASM of the sternomastoid muscle produces characteristic alteration of head position. The condition of the spasm may be constant or intermittent—that is, there may be a fixed spasm of the muscle which will persist without relaxation for extended periods of time or there may be intermittent spasms which vary from time to time and the contractions may occur as often as many times a minute, so that the changes of head position resemble a tremor.

Torticollis of Peripheral Origin.—The spasm of the muscle is due to a disorder in innervation. The defect may lie in the peripheral reflex arc and be due to some form of inflammatory lesion affecting either the muscle itself or the segments or peripheral nerve trunk supplying muscle. Occasionally the spasm may be a compensatory reflex, such as occurs in certain types of extra-ocular paresis or imbalance. Instances have been described in which the stimulus resulting in the muscle spasm apparently originates in the vestibular apparatus.

The muscle spasm occurring under the above-listed circumstances is usually more or less fixed and does not vary materially.

Torticollis of Central Origin.—There is another type of torticollis, which is the subject for this discussion. I refer to the abnormal contractions of the sternomastoid muscle which may or may not be accompanied by similar contractions of adjacent muscles. This sort of torticollis can be classed as of central origin and represents the end-result of stimuli which may originate either in the cerebral cortex (which may be

structurally perfectly healthy) or arise out of some structural or physiologic alteration of function in the basal ganglia.

Torticollis of central origin shares with certain other types of abnormal movement the tendency to vary with alterations in the patient's state of mind. That is, not only the direction of attention will have an influence, but the degree of emotional tension or imbalance will alter the degree to which the muscle spasm manifests itself.

The torticollis of central origin may be the result of certain primary nervous system infections. In particular, *epidemic encephalitis* is known to produce the symptom.

Is It a Physical or Psychic Manifestation?—Neuropsychiatrists vary in their judgment as to whether the symptom should be classed as a tic, or as an expression of some defect in the physical sphere rather than the psychological. Those who are organically minded stress the instances of cerebral infectious disease, and point to the cases in which torticollis is an early symptom of true dystonia. The physicians who stress the psychic sphere call attention to the cases in which the symptom is a physical manifestation of mental maladjustment and not only draw the analogy with the various movements known as tics, but may even go so far as to attempt to describe specific mental mechanisms which condition the muscle spasm.

A number of cases of torticollis have been selected, classed into certain sub-groups, and the possibility that these various types of centrally originating torticollis have a common ground or origin may be revealed.

Identity of Certain Abnormal Movements Resulting from Physical or Mental Cause.—It should be kept in mind that sometimes there is an impossibly fine distinction between abnormal involuntary movements due to a lesion and movements which apparently are voluntary or psychogenic in nature, in that they not only originate in the cortex but occur under circumstances which imply that the precipitating cause is an emotional imbalance. The psychic defects in patients with a dystonia have furnished ground for much discussion as to the relationship between the physical and psychic manifestations of the disease. Patients who have recovered from rheumatic chorea are known to be prone to experience recurrence of the abnormal involuntary choreiform movements when the environ-

ment has been unfavorable and responsible for mental maladjustment. Certain writers have commented upon the identity of certain abnormal movements resulting from either physical or mental cause, and there has been speculation as to whether some individuals are so built that psychic stress may produce phenomena which are in other instances a sign of structural changes in the basal ganglia. Those of us who saw many of the patients with acute epidemic encephalitis in 1919 and 1920 were struck by the instances in which the expression and posture were remarkably similar to what had long been familiar in catatonia. The "decerebrate" limb postures which occur in certain patients with conversion hysteria are illustrative. There are also the cases in which so-called "compulsive movements" and tics are part of a clinical syndrome which includes various objective evidences of true structural degenerative disease of the nervous system.

GROUP I. TORTICOLLIS IN THE APPARENTLY PSYCHONEUROTIC

Case I.—This patient was first seen by me about 1924 and had a spasmodic torticollis which was accompanied by various associated abnormal movements of the shoulders and other neck muscles. She was an overly tense and conscientious clerical worker who had become a secretary to a corporation officer. She had always been subject to tics and was a nail biter in childhood. The torticollis began after she had been under particular tension in connection with her work. She happened to have a bad pair of tonsils and there was a history of cervical adenitis. Removal of the tonsils resulted in transient benefit to her torticollis. She did not recover for several months and her recovery was parallel with the easing of her situation at the office and the regaining of a feeling of security and confidence in herself.

About 1929 the patient returned with another attack of torticollis which was preceded by a period of anxiety about some personal matters. This attack lasted several months and recovery paralleled the clearing up of the reason for emotional tension. In 1936 the patient had a third attack of torticollis. This time, there were so many abnormal movements of her limbs that she became unable to stand and her clinical picture might very easily have been regarded by an uninformed observer as characteristic of a severe form of degenerative chorea. The patient recovered from this episode.

This patient had a cousin with a similar disorder.

Case II.—This patient was a twenty-three-year-old college graduate who had been an honor student and captain of the swimming team at college. He had neurotic parents and had always been supervised very carefully. In the fall after he graduated he became tense and upset about his job and began to jerk his head to the right. He complained of some pain in the left side of the neck. Over a period of several months he was shunted from one doctor to another and infected tonsils and offending teeth were extracted. Although the neck discomfort disappeared, the torticollis continued and not only fluc-

tuated widely but its variations were coincidental with what seemed to be adequate emotional turmoil. Eventually the family and the patient seemed to come to an agreement about what should be done and it was decided that the patient would go to a sanitarium for psychotherapy. The torticollis got worse before this plan was put into execution and another look at the patient's mouth revealed a dental abscess and this tooth was extracted. Recovery occurred within a few weeks.

There might be a serious question as to my classification of the second patient's torticollis as a manifestation of a psychoneurosis. As with the first case, focal infection played some part, perhaps in the initiation of symptoms. However, the disappearance of pain and the absence of any myositis or adenitis although the head movements persisted, and the type of fluctuations, lead me to class the abnormal movements as outward manifestations of variations of emotional tension.

GROUP II. TORTICOLLIS IN PERSONS OF PSYCHOTIC TYPE

I have only one patient in this class to describe:

Case III.—This patient was a thirty-seven-year-old married man who gradually over a period of several months developed a severe torticollis with a superimposed nodding tremor of the head and became so conspicuous in his performance that he preferred to remain indoors. He had possible focal infections attended to, tried short vacations, consulted irregular practitioners, and eventually became so emotionally unstable and depressed that a psychosis was feared by the relatives.

In my study of the patient and during the seven months during which he was under my care, I found that the situation involved two apparently equally important factors. First was the *family history* of nervous and tense and worrisome parents, with a maternal heredity of two individuals who had developed "nervous breakdowns" in the fourth and fifth decades, and then in the patient himself his personality prior to the onset of symptoms was that of the overconscientious, meticulous, worrisome person who on several occasions had been through what in retrospect strongly suggested a mild depression of manic-depressive character. Second was the evidence that he had for about two years before his illness commenced been under special *strain* and worried lest his new responsibilities incidental to a promotion be not acceptably lived up to. Psychotherapy seemed to be responsible for the patient's recovery. Three

years later, the patient had a mild recurrence of torticollis at a time when he had again become apprehensive over his work.

GROUP III. TORTICOLLIS AS PART OF A GENERALIZED NERVOUS SYSTEM DEFICIENCY

Case IV.—I first saw this patient in 1920. She was a school teacher and for several years had been subject to a coarse tremor of the fingers, occurring at rest, increased when under tension, but not interfering with the use of her hands (the tremor disappeared during writing, using table utensils, and in handling playing-cards). In 1922 she developed a spasmodic torticollis at a time when she had a clandestine affair with a man of another race. The patient was red-haired and blue-eyed and of Anglo-Saxon stock. She had always been attracted by dark-complexioned males and had indulged in promiscuous sexual relationships with a Turk, a Persian and men of Negro blood. The clandestine affair which was coincidental with the torticollis onset involved the fear of discovery.

Several years went by and I again saw the patient in 1930. By this time she had become definitely deteriorated, had had to stop teaching in 1927, and she was full of abnormal involuntary movements. She eventually went to a state hospital and is regarded as an instance of degenerative chorea.

Case V.—This woman had been troubled for six years with a torticollis and incoordinate movements of the hands. Her symptoms began a few months after her marriage. The patient had initiated the courtship by writing letters as a "fan" of the gentleman in question. The romance immediately resulted in disillusionment and the couple quarreled before they parted company. The patient had been a governess and a music teacher and gradually became unable to work at either occupation.

Closer inquiry into the patient's previous history showed that incoordination in the use of her hands first appeared when she was ten years old and that at the age of twenty-five there were occasions when she manifested abnormal head movements. She had always been emotionally unstable and did not persist in any objectives and although she had a college education she contented herself with being in a dependent position.

The patient had a generalized hypotonia, a very high, narrow palate, a marked dorsal scoliosis which from the history could not be traced to any illness or injury, and the broad, high-arched feet with hammer-type toes which frequently are regarded as stigmata of developmental imperfection.

Of interest in this patient was the fact that a younger sister had similarly shaped feet, was very loose-jointed, and did not get along well in her environment. The patient's father was a physician whose drinking habits and marital career implied that he had none too stable a make-up.

In this patient, there was no apparent rheumatic or focal infective factor. Her appendix, tonsils and adenoids were re-

moved when she was eight years old and she never had any illness suggestive of infectious chorea.

COMMENT

Innate Predisposition as a Factor.—When one speaks of symptoms as being of organic character, one implies either a structural or physiologic defect in tissue. The defect may be the result of some cause operative during embryonic development or after birth. Another influence which cannot be overlooked is the hereditary factor. We are familiar with the hereditary factor in allergy and migraine which are functional or physiologic rather than structural diseases. We are familiar with the constitutional factor in diabetes, thyroid disease, gastric ulcer and gallbladder disease—in all of which conditions one finds some morphologic correlates. With respect to diseases of the nervous system, the hereditary influence accounts for a large percentage of the personality defects which lead to the constitutional psychoses. Of more definitely structural character are the heredo-degenerative and familial diseases. In this group are such conditions as the amauroses, the hereditary forms of ataxia and certain other unusual syndromes, such as the so-called "familial tremor." Of less definitely defined structural nature and probably of physiologic character are some of the metabolic disorders. Progressive muscular dystrophy is a good illustration. In fact, the group of myopathies is regarded by some workers as illustrative of some presumably hereditary defect.

In other words, when one thinks of a disease as possibly "organic" in character it might be wise to consider whether an inborn predisposition plays any part.

It has long been recognized that the individual subject to tics and phobias possesses certain personality traits or defects, particularly in the emotional sphere, and that such outward manifestations as the tic are signals of some inward emotional tension. Accepting this generalization as reasonably correct, one might regard a tic as a manifestation of a predisposition to react in a particular way under appropriate stress. This conception would not interfere with the possibility that in certain instances a tic can be traced back to a movement which in

the beginning had some useful purpose. The very fact that the movement is continued after its legitimate use is gone, or that the same tic movement may reappear at a later date, is consistent with a difference in innate reactivity and the symptoms as a combination of predisposition plus the environmental or acquired stress. At this point, I will refer again to the individuals who have recovered from infectious chorea but on later occasions may display the same choreiform movements as the manifestation of some stress which apparently breaks cortical control over lower motor integrative arcs.

A Critical Study of the Cases Presented.—The cases of torticollis which have been described include individuals who at one end of the spectrum or scale have not shown any progressive or permanent symptoms or signs of congenital, structural nervous system disorder. Two patients had focal infection which seemed to have something to do with the onset of symptoms, but in both cases there was psychic maladjustment and in one patient the torticollis was recurrent. In a third individual, there was a family history of mental disorder and the patient himself had an unstable make-up with a tendency to feel inadequate and insecure.

At the other end of the scale are the two patients whose torticollis was but a fraction or fragment of a more generalized nervous system deficiency or dysfunction. One patient not only had anatomic stigmata, but a sister who apparently was similarly affected in a lesser degree, and a father whose career implied that he had a psychopathic make-up. This patient manifested other disorders of movement of involuntary character. The other patient had a variety of sex perversion and eventually became unable to earn her living in a learned profession. From a somatic standpoint, there was an accompanying motor disorder in which torticollis and head tremor were prominent and the outcome after a period of several years was mental and physical incapacitation requiring institutional care.

The one thing which all these patients had in common was torticollis. In every instance, there was some degree of mental or emotional maladjustment. In two of the five cases, there was very definite family history of nervous system or personality defect.

CONCLUSIONS

It is my idea that the torticollis in all these patients represented a specific type of abnormal involuntary movement which might be released under various circumstances and that the causes may lie on one end of the scale purely in the psychic sphere and at the other end of the scale in a physical disease or even a developmental defect which produces structural changes in the brain. With respect to the latter type of case, neuropathologists do not know either the locus of or character of the lesions which are definitely responsible for the particular abnormal movements.

One must look further than the apparent *precipitating* cause for the origin. We are familiar with the cardiac and gastro-intestinal neuroses, which occur in some patients whose constitutions have a reduced tolerance for physical or psychic stresses. Other individuals, subject to the same precipitating stresses, do not develop these somatic manifestations of vegetative nervous system imbalance. The simple fact that torticollis is not an inevitable or constant result of the various stresses associated as precipitating causes requires thought as to whether there is ever any predisposing factor.

Therefore, it seems unnecessary to quarrel about whether in a given patient the torticollis movements themselves are of organic or psychic origin. One patient may really be suffering from a psychoneurosis. Another may be suffering from a physical disease without any personality impairment or psychoneurotic factor. Torticollis is a symptom rather than a disease, and is a manifestation of a regional structural or physiologic defect. This defect may be a sign of a more generalized nervous system instability, which often may be due to hereditary or congenital fault.

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CACHEXIA (ANOREXIA) NERVOSA*

Historical.—With that admirable clinical astuteness shown by the early English physicians, Sir William Gull[1] first described and named the syndrome of anorexia nervosa in 1868. He described a disease rare in males, which occurred usually in young girls from sixteen to twenty-three with resultant severe emaciation, amenorrhea, changes in temper and associated remarkable physical energy. He considered this disturbance was due to a "morbid mental state." Its great frequency in the female was stressed by a Frenchman whose understanding of its feminine connotations induced Lasègue[2] to call it "hysterical anorexia."

The passage of time permitted a serious oblivion to creep over this important syndrome and when Simmonds[3] in 1914 described the syndrome of hypophyseal cachexia resulting from destruction of the pituitary gland, a new factor was injected into the symptom of emaciation. Similar reports were noted thereafter and these cases were presented as recovering from Simmonds' disease by virtue of this or that glandular injection or oral medication. On the other hand, those cases of this disease which came to autopsy showed a serious destruction of the anterior lobe and associated simple atrophy of the thyroid, adrenals and gonads. Bratton and Field's[4] as well as Aitken and Russell's[5] cases likewise show this finding. The well-known pluriglandular insufficiencies of Claude and Gougerot[6]

* Submitted for publication in June, 1940.

and of Falta[7] have begun to take on a new clinical significance and their understanding a new revision as the result of a modern conception of this syndrome. However, patients suffering from Simmonds' disease by the nature of their illness do not recover and usually live for a varying number of years before death finally claims them. As more autopsied cases of this disease were reported it was more and more evident that the striking note in these cases was a progressive and severe lassitude, weakness associated with somnolence and sometimes organic psychotic trends, while marked aging of the tissues with atrophy of the breasts and falling out of the pubic and axillary hair were evidence of a secondary hypogonadal and hypothyroidal deficiency.

Anorexia Nervosa Differentiated from Simmonds' Disease.—Of recent years there has again been an awakening of interest in anorexia nervosa and the author, though recognizing the entity as described in the literature by the early writers, has been confused in his approach by too great insistence upon glandular diagnosis and therapy, with resultant prolonging of the therapeutic achievement. As more and more specific cases with evidence of lack of response to endocrine products, both before coming into my hands and after came to my attention, I began to study etiology more carefully. There then appeared a mass of psychogenic material which, as it was elaborated, proved to be a competent exciting cause for the disease; and then it was observed that the clinical picture itself had distinct differences from that described by Simmonds.

It occurred especially in young, unmarried women, or as Birley[8] suggested, in young married women who had never borne children, while pituitary cachexia occurred in middle life often as the result of infection or too many pregnancies. The loss of weight is greater in anorexia nervosa, while it is sometimes seen in Simmonds' disease only as a terminal event. On the other hand, aging of the tissues, falling of the hair, and atrophy of the sexual organs are not seen in the functional disorder though pathognomonic of pituitary destruction. Turner[9] has recently tabulated statistically the reported cases of Simmonds' disease and anorexia nervosa and the most noteworthy differences brought out by him were that the former showed an incidence of two to one, as against four to one female; an age

limit of twenty to sixty as against ten to forty, with an amenorrhea of 51 per cent as against 86 per cent; and 100 per cent mortality as against 6 per cent mortality in anorexia nervosa.

The most striking differences lay, however, in the field of the psyche. The early writers were practical and searching in their common-sense psychology. Gull's[1] original concept still stands undisputed, namely, that anorexia nervosa is a morbid mental state. Lasègue[2] in 1873 stressed the contrariety of the patients, some of whom may have suffered from thwarted love affairs and jealousy. Their mothers were often too wrapped up in the daughters and needed treatment also. Often these were unhappy in their sex life with sexually weak or impotent husbands and hence turned their love upon the daughter. The child was smothered with mother love and was unable to take the place due her at her age, and often experienced an accompanying serious restriction of her liberty.

Recently Langdon Brown[10] remarks of the fear of growing up and facing adult responsibilities, with an undue dependence on the father and hostility toward the mother. He mentions the possibility that dementia praecox lurks behind the shadow of anorexia nervosa. He quotes Sir Arthur Keith as saying in the discussion that "a tendency toward carrying youthful characters into adult life had played a large part in the evolution of the human race." This, however, could be a source of weakness and when it was irregularly or ill developed, it produced incomplete personalities. Anorexia nervosa was a difficulty in growing up. Other significant English contributors on the subject have noted the modern mode for "slimming" and "maiden modesty" and the desire to have small breasts, as a cause for reduction in diet. The close relation of the appetite to sexual desire, and the hatred of bodily functions, looking upon them and sex feelings as esthetically low and feeding as a "gross business," has been a related background in certain of these cases of refusal of food and so-called anorexia. These patients usually had a "dead look" relating to their parents and by means of their illness they had maintained a dominant role over the household and the parent. Their undiminished, almost excessive vitality has been noted by all and is in striking contrast to the lassitude of the true Simmonds' cachexia.

Medical reports on these cases, almost without exception, have warned against "deep, exhaustive psychological exploration." They make light of the fundamental psychology and feel that proper regimen, persuasion and common sense will suffice. With this point of view I can have little sympathy. One writer says, "the difficulties are of trivial nature," and then remarks that these patients often persist in utilizing their refusal of food at the demand of their own inner purposes, "sometimes even unto death."

In a recent discussion of this disease before the Royal Society of Medicine, Ryle, Sheldon, Spence and Hurst[11] made significant observations on this syndrome. They noted that not until the description of Simmonds' disease was there confusion regarding this clinical picture and since then many physicians abroad were describing anorexia nervosa as the graver pituitary cachexia. Sheldon noted the similarity of the syndromes but found a point of difference in hirsutism which is common in anorexia nervosa but has never been described in Simmonds' disease. He states that in the Irish potato famine of 1845, hair an inch long on the faces and arms of children was described—an adaptation of the body (adrenal cortex overactivity) to starvation conditions. This finding has been strikingly noted in the majority of my reported cases, and is I believe a diagnostic factor of considerable importance in the more severe cases.

ILLUSTRATIVE CASES

With much interest I observed the following cases until it was well determined what their outcome would be, and they are reported in as much detail as seems wise in order to give a full understanding of the condition.

Case I.—H. W., a twenty-one-year-old school teacher.

History.—In January, 1933, the patient complained of not being able to eat, although hungry at times. If she did eat a full meal, she could not eat again that day. She fills up very quickly and gets a pain in the stomach and occasionally vomits foam. She feels shaky and weak, and has lost all interest and is depressed. The condition has persisted for one year. The patient teaches school and wonders if she is doing it adequately. Menses began at eleven years of age, and were often scanty, lasting three to four days. They stopped a year ago after being regular.

Examination.—The patient was thin, emaciated in appearance, and weighed

80 pounds. She had pale, cold, mottled extremities, dry skin and hair, and a narrow palate with maxillary torus. The blood pressure was 105/65 and the basal metabolic rate —22 per cent. x-Rays showed a normal skull and sella turcica, and the urine revealed an absence of ovarian hormone.

Course.—The patient gradually gained weight when she made herself eat and in one and a half years had gone to 102 pounds. The breasts were en-

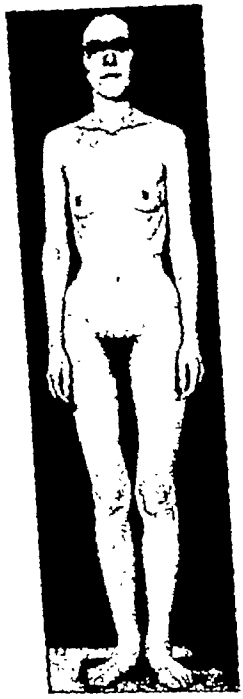


Fig. 62 (Case I).—Appearance of patient H. W. at time of examination.

larging. Her basal metabolic rate was +12 per cent; but she gets tired and dragged at times. She was married soon after this and reported by letter that she was well.

Case II.—K. R., a twenty-six-year-old woman.

History.—The patient began to lose weight in January, 1932, gradually falling from 117 to 90 pounds. She was admitted to the hospital on August 31, 1936, weighing 87 pounds. Four years before, she had developed a fear that she would become masculine. This was related to the irregularity of her periods which finally stopped two years ago. There have been no menses since.

On admission to the hospital the patient admits that she avoids eating because she has no interest in it. She is depressed and unhappy and feels very desperate. Her past history shows a family situation in which there was great overprotection on the part of both parents. She was very shy and ill at ease as a child, and was only really happy when she was with her brother. She

was very devoted to him and was distressed when he married a girl whom she thought was unworthy of him. She had a strong brother fixation and resented the restricted family life. She was a quiet, mousy person who always said precisely what she had been brought up to say by her mother. Her father always wanted her chaperoned and her ideals were of the highest.

Examination.—The patient is tall, of narrow build, cadaveric in appearance; the breasts are well developed; there is masculine pubic hair; no thyroid enlargement and no aging of the tissues.

Course.—The patient spent five weeks in the hospital during which time there was slight improvement in depression and no gain in weight. After leaving the hospital she entered upon a secretarial course, took a job with a new interest, and began to grow away from the parents and to obtain some emancipation of thought. She reported one year later weighing 118 pounds; her morale was excellent and she no longer had the depressed, desperate feelings.

The menses have now returned regularly. She is still working and weighs 130 pounds.

Case III.—E. H., a nineteen-year-old woman, a college student.

History.—During the previous two years the patient had lost 20 pounds and developed amenorrhea. She was cheerful and active, and said she ate well but the mother, who always accompanied her, said she ate like a bird. The mother was very worried about her and had taken her to several physicians who, because of a —24 per cent basal metabolic rate, gave her thyroid and pituitary. Her weight then was 81 pounds, and she gained a few pounds but the menses did not return. The mother brought her in to see me and with insinuating voice, persuasive manner, and noble purpose, definitely annoyed her daughter who sat with obvious disinterest in the proceedings and said she would do what she was told. She later confided to me that food was not interesting, and that she was much oppressed by her college course. Her mother was too overprotective, very nervous, and always waiting anxiously for some one of the children to be sick. This daughter obliged and later admitted it was because she did not want to grow up and away from the parent.

Examination.—Physically this girl was thin, somewhat emaciated and weighed 90 pounds. The hair was dry and the mammae were small but not atrophic. The vulvae were rather large but the external genitalia otherwise were normal. The basal metabolic rate was —20 per cent. *x*-Rays of the skull were normal, and ovarian hormone was absent from the urine.

Course.—The patient was put to bed and on a regimen at home, but she gained only 5 pounds in a month. She was then allowed to go abroad for the summer, away from the family, and she returned having gained 15 pounds. Finally, after one and three quarters years she weighed 115 pounds. The menstrual periods had been regular. The basal metabolic rate was +3 per cent. A significant factor which undoubtedly contributed to the recovery was the unexpected death of her mother. The patient, though grieved, has been definitely relieved of conflict since and is now cured.

Case IV.—E. W. R., a thirty-one-year-old housewife, complains of loss of weight during the past three to four years. She loathes cooking and the sight of food. Her stomach quivers with food and almost daily she has a fleeting attack of colitis. She has been married ten years, but after a year she separated from her husband because he did everything he could to belittle her.

She left him to take up nursing training. For three years her health was good and she weighed 126 pounds. Then she and her husband began living together again. He is loyal to her but completely unsatisfactory. He will often not speak for two hours at a time. Sex life is incomplete and she has no orgasm except occasionally in her sleep. Now her weight averages in the low 90's and her blood pressure is 90/55; she has a narrow chest and pelvis, scanty hair, small breasts and in general a hypoplastic status.

The aversion to food in this case is definitely related to her husband. She has passed from observation and no reports as to her progress have been received.

Case V.—A. S., a thirty-year-old woman.

History.—At the age of eighteen the patient weighed 130 pounds. Prior to 1927 she had been happy in her family life, but very spoiled in it. She

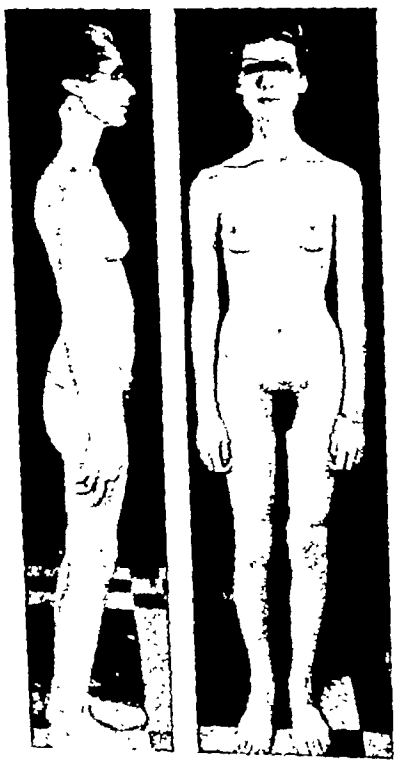


Fig. 63 (Case V).—Appearance of patient A. S. at time of examination.

was the idol of her parents and her boy friend, whom she adored. At this time, she met her future husband, and although it distressed her to hurt her friend, she took her husband-to-be away from her cousin, who was very

attractive, and, she thinks, married him for spite. The breakdown came on during this conflict over her affections toward these two men. Her husband proved to be domineering, expected her to be a housebody, and hurt her over and over again. He was jealous of her parents (rightfully, no doubt) and drove her back to them in spirit. Her sex experience with him was mechanical, and neither cared much about it.

In January, 1928, the patient had a severe cold, and afterward began to feel run down. She suffered from indigestion and was afraid to eat because food upset her stomach. Loss of weight began at about this time, and the menses became scantier and irregular. Soon they ceased entirely and the weight gradually dropped below 90 pounds. She has had several series of endocrine treatments with antuitrin "S," progynon and eschatin. She was told that her basal metabolic rate was —40 per cent, and was given 4 grains of thyroid daily.

Examination.—The patient on admission to the Neurological Institute appeared cadaveric: weight 85 pounds, hair and skin dry, myxedema, small mammae with no atrophy, hypoplastic build, and striking cachexia.

There was a low basal metabolic rate of —25 to —30 per cent, an absence of ovarian hormone, and no other significant laboratory findings. The sella turcica was normal. The chief complaints were gastro-intestinal, with gas and a feeling of fulness, a dragging sensation accompanied by apprehension and depression, and great concern over the continued constipation, which no cathartic relieved. She feels hungry, but will sit down to food and fear to eat, because it will make her so uncomfortable. There is an agonized pulling of the intestines, and a spot in the stomach through which food will not go, also much gas. When she was first sick, she would at times dispose of her food surreptitiously, to give the impression of having eaten it.

Course.—During two and one half months at the hospital, the patient increased her weight from 85 to 103 pounds. There was no endocrine therapy given.

This patient has a strong family attachment, an incomplete sex relationship with her husband, and an obsessional neurosis with an idea fixed on her gastro-intestinal tract. Resolution of her psychological factors was strongly resisted.

She is still under psychotherapeutic treatment, and recovery is progressing favorably, though the periods have not returned yet. The pluriglandular syndrome was secondary to the nutritional disturbance and psychoneurosis.

Case VI.—D. P., a twenty-six-year-old woman, was admitted to the St. Luke's Hospital in 1934.

History.—Five years previously the patient had had measles (1929), with which she was very ill. She was prostrated afterwards, and had regurgitation and cardiospasm for three weeks. Before this illness her weight was 112 pounds; afterwards she was well but tended to be constipated. This was preceded by progressive loss of weight, nausea, vomiting and weakness. The patient was married in 1930 for two days and then had her marriage annulled on the grounds of fraud. Following this, she had considerable stomach trouble with gas, spasms, watery stools and frothy movements, associated with redness of mouth and uvula and fever.

In November, 1931, she had been admitted to the Neurological Institute for a week's observation. Her weight was 72 pounds; basal metabolic rate —33 per cent; she complained of cold hands and feet, waves of nausea, and sweats and nervousness. The diagnosis was pluriglandular deficiency (Sim-

monds' disease). She was removed from hospital by her father, a physician, who did not approve of the treatment. Shortly thereafter she was at the Doctor's Hospital with a diagnosis of hypothyroidism, but no treatment was given except thyroid. Later she saw many doctors. She had a negative gastro-intestinal x-ray series, but was said to have slight secondary anemia and a basal metabolic rate of —13 per cent.

When the patient entered St. Luke's her complaints were loss of weight, amenorrhea, constipation, poor digestion, nausea, gas, and difficulty in taking food. Her menses began at eleven or twelve years of age but had been absent for the past year and a half. All her teeth had been removed because of a mouth disease in 1932.

Examination.—On admission the temperature was 96.2° F., the pulse 62, the blood pressure 90/62 and the weight 62 pounds. The skin was delicate and fine; small breasts and no subcutaneous tissue. The skeleton seemed to be covered with nothing more than skin, but there was no falling of hair or aging of tissues. There was marked coldness of the hands and feet. The laboratory findings showed a normal sella turcica; blood sugar 83 mg.; calcium 10.7 mg.; bleeding time 4 minutes; clotting time 5 minutes; red cells 3,250,000; hemoglobin 70 per cent; white cells 5,300; polymorphonuclears 34; lymphocytes 62 and platelets 130,000. The Kahn test was negative, and the basal metabolic rate was —40 per cent and —19 per cent.

Course.—The patient remained in the hospital one month, during which her weight varied between 59 and 66 pounds. During this time she would not eat while the nurse was in the room. If she was left alone the trays were always emptied, and the nurse observed through the keyhole that she was disposing of the food by throwing it down the toilet.

The patient was again removed from the hospital by her father against advice because the diagnosis of obsessional neurosis with secondary pluriglandular insufficiency was made. She had a close family attachment, with affection for the father and absorption by the mother, whom she kept thoroughly punished by her illness. Recovery was prolonged and not followed by me.

Case VII.—K. W., a twenty-five-year-old woman, was referred because of extreme exhaustion and cachexia.

History.—Since the age of seventeen the patient had been gradually limiting her diet in order to avoid indigestion, a "loggy" feeling, burning, belching of gas, and the feeling that there was some stoppage in the intestines. She experienced great fear and anxiety in regard to her indigestion. She gradually lost weight from 133 pounds until, on her admission to the hospital in May of 1936, she weighed 82½ pounds. At this time there had been amenorrhea for three years.

Examination.—On admission, the patient was cadaveric, nervous, emotional, depressed, constantly talking about food, picking at it, practically going through a ritual in eating, washing down each mouthful, and actually consuming very little food. The laboratory examinations were entirely negative except for a basal metabolic rate of —25 to —30 per cent, and an absence of ovarian hormone in the urine.

Course.—Prior to her admission to the hospital, the patient had been treated with antuitrin "S" and estrogenic hormone for over six months without improvement. During her stay in the hospital, she increased her weight from 82½ to 112 pounds on regimen and psychotherapy.

Her psychotherapeutic treatment brought out the important fact of a

very serious conflict in childhood with her mother, and a definite father fixation. She had repressed all feelings in childhood, so it became a habit with her. She was never able to enjoy pleasure of any kind, including sexual, because in her early life the enjoyment of any kind of pleasure had always been squelched by the family. There are some interesting factors in this, in that starving gave her a sense of exhilaration. The sense of hunger was associated with masturbatory feelings, and there was a definite diversion of her sexual feeling away from the genitals toward oral erotic reactions. She now weighs 115 pounds, menstruates regularly, and is married, and one year after is to have a child.

This is another patient who presents the picture of a severe psychoneurosis, associated with fear and anxiety and a gastro-intestinal obsession ending in loss of weight and a serious pluriglandular deficiency, who made a recovery under psychotherapy.

Case VIII.—D. W., a fourteen-year-old girl, was referred through the courtesy of Dr. Charles G. Kerley.

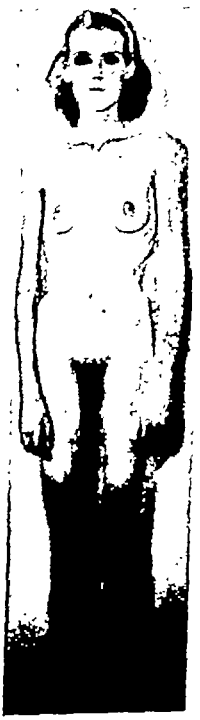


Fig. 64 (Case VIII).—Appearance of patient D. W. at time of examination.

History.—Two years ago the patient had a mastoid operation followed by a gain in weight to 140 pounds. A year and a half ago she began to lose

weight, about 2 pounds a week. She lost the desire for food, and occasionally was nauseated and vomited. Food caused epigastric discomfort so she did not eat. At times she craved food, but could not satisfy the craving. She lost weight progressively down to 79 pounds. Menses had begun at eleven, and were regular until two years ago, when they became irregular and skipped. Amenorrhea began fourteen months ago and has continued to date.

Examination.—The patient is a thin, cachectic young girl, with good maturity, and breasts well formed. There is considerable hair growth on the arms and legs, and some on the face. The patient is restless and overactive, and can hardly remain in bed. Laboratory data: glucose tolerance curve, 66, 104, 91, qns, 51, 45; slight anemia; nonprotein nitrogen 16 mg.; basal metabolic rate —37 per cent; skull and sella turcica normal under *x*-rays. Hormone studies: follicular (ovarian) hormone, no R. U., follicle stimulating hormone, none.

Course.—The patient made a slow, gradual gain in weight, without endocrine medication, until she reached 96 pounds. At this time, after two months, the patient developed acute appendicitis. At the operation by Dr. E. J. Donovan, the ovaries were found to be somewhat small and pale in appearance. A specimen of the right ovary was excised and histologic examination revealed a normal gland.

This child has made a complete recovery, having learned in the hospital to be independent of her family and acquired enough maturity to enjoy it. She is the youngest in the series and the mechanism of her neurosis was very simple, and recovery easier.

Case IX.—M. D., a nineteen-year-old woman, was admitted to the Neurological Institute March 3, 1939.

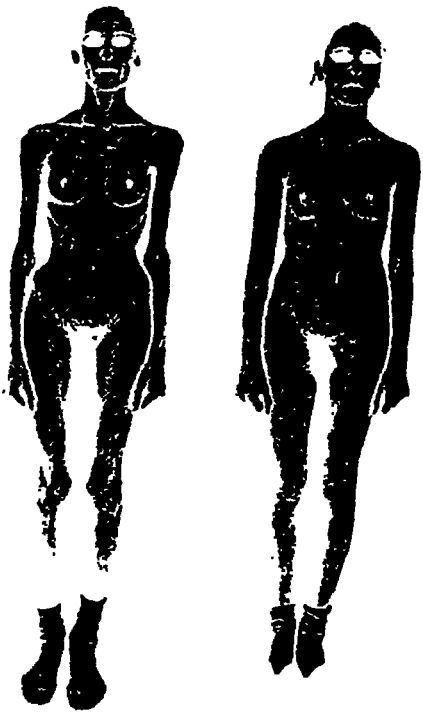
History.—The patient had weighed 115 pounds three years ago. She was reported acting peculiarly and dreaming at school over a firm attachment to a teacher. There were implications at that time of homosexual behavior, but there was none. One year ago she began to refuse food and to lose weight. She lost 70 pounds in six months, and amenorrhea began one year ago. She complained of weakness and depression, but was restless and active. Her family physician gave her cortical hormone and pituitary *x*-ray treatments. After this an excessive growth of facial hair was noticed. She has a feeling of fulness in the stomach and vomits often. She says that she eats but really does not. She has continually masturbated since the age of eleven or twelve years, and has a deep sense of sin and guilt about it. Though brought up in her family's religious faith she does not believe in it, and is having it forced on her by her mother and aunt. She is resentful against them. Her aunt bosses her and they all are at her continually about eating, so that her rebellion became more and more centered about her food. She was depressed, cried readily, was seclusive, talked little and showed marked restlessness while in the hospital; remaining in bed was torture to her. She looks down upon her parents as inferior and "middle-class," and she has built a wall about herself so that she has no feelings and no interests.

Examination.—Marked emaciation, hair on face, arms and trunk. Dry skin. Mammae full. Sclera rather bluish in color. Blood pressure 80/60. Slight anemia. Blood cholesterol 112 mg. Phosphorus 2.9 mg. Blood sugar curve 78, 74, 140, 141, 147, 103. Basal metabolic rate —44 per cent, and —21 per cent a week later.

Course.—During the patient's stay in the hospital, her cooperation was finally secured and she gained 33 pounds in weight, up to 106 pounds. The

hair on the face practically disappeared and she left the hospital to continue psychotherapy and reeducation which was badly needed in her home life and relations. She has fluctuated up and down since discharge, but is doing part-time work pending further emotional readjustments.

Here again is a pluriglandular syndrome secondary to starvation in a distinctly neuropathic type, whose whole mental life is distorted and unstable,



Before After

Fig. 65 (Case IX).—Appearance of patient M. D.

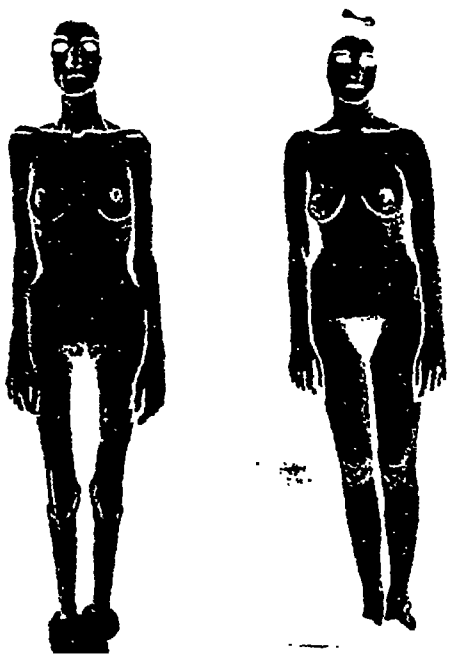
the starvation being only one way of punishing her parents for their extremely bad handling and for trying to maintain her in the child relation.

Case X.—T. F., a nineteen-year-old woman, was admitted to the Neurological Institute April 25, 1939.

History.—The patient's illness began eighteen months ago upon the institution of a regimen to lose weight, then 136 pounds. About the same time she had a severe emotional shock when her sister married her fiancé. She began to vomit and weight loss was rapid, down to below 70 pounds. She went to another hospital on four occasions, and each time upon returning home she became worse. She had an exploratory laparotomy without avail

and finally she was operated upon for a right adrenal tumor but none was found. Extensive endocrine therapy was given without result.

Examination.—On admission to the hospital the patient weighed 62½ pounds, and was thin and emaciated, with generalized hirsutism. The skin was dry and pale, almost cyanotic in hue, and the scleras were blue. The tongue was smooth and red and there was a gingivitis. The thyroid was palpable and the abdomen scaphoid. Laboratory studies: hemoglobin 50 per cent; red blood corpuscles 2,920,000; white blood corpuscles 8,600; blood sodium 135 mg.; potassium 2.9 mg.; calcium 10.8 mg.; cholesterol 171 mg.; blood sugar curve 85, 126, 103, 87, 78, 82; basal metabolic rate —44 per cent;



Before After

Fig. 66 (Case X).—Appearance of patient T. F.

follicular (estrogen) hormone almost absent (2 R. U.). The intravenous pyelograms were normal. Gastric analysis showed achlorhydria and the patient was given nicotinic acid therapy (500 mg. daily). On this she showed a marked reticulocyte response.

Course.—Psychically the patient was depressed and shut-in, and obstinate in her refusal of food. She vomited when forced to eat. After one month she began to cooperate by taking liquids, and later solids. The weight went up to 107 pounds, and then, when discharge was proposed, she was sullen, antagonistic and vomited again. She finally was discharged to a family to do housework away from her home surroundings.

This is the picture of severe cachexia coming on as a result of a "getting

thin complex" and a serious emotional frustration. The clinical picture of a pluriglandular deficiency combined with a hypertrichosis suggested adrenal exploration and glandular therapy—all to no avail and to the chagrin of the therapeutists. Readjustment and a careful dietary regimen brought about a recovery.

THE CLINICAL PICTURE

Physical Signs.—The above group of patients have as their outstanding sign a severe *cachexia.* Loss of weight is caused by an unwillingness to eat based upon either conscious or upon neurotic avoidance. Actual loss of appetite is a rare occurrence. There is really a refusal of food because they will not eat for fear of discomfort after eating or for fear they will not remain slim. For these reasons the author objects to the long-accepted term, "anorexia nervosa," and suggests "cachexia nervosa" instead. Hysterical anorexia has a similar background and, although the term cachexia nervosa does not perhaps tell the whole story, it suggests the dominant presenting picture. The symptom of cachexia is definitely a sign of malnutrition with which is associated a group of secondary somatic manifestations, largely endocrine.

TABULATION

THE CLINICAL PICTURE IN CACHEXIA NERVOSA

Physical Signs	*Psychoneurotic Manifestations*
1. Cachexia.	1. Gastro-intestinal obsession, refusal of food, vomiting, indigestion.
2. Amenorrhea. Absence of estrogenic hormone.	2. Anxiety and fear.
3. Dry skin—low basal metabolic rate −30 to −40 per cent without increased cholesterol.	3. Depression and hopelessness.
4. Hypertrichosis rather than falling of hair.	4. Suicidal impulses (death wish).
5. Absence of genital atrophy.	5. Family fixations and antagonisms.
6. Gingivitis and glossy tongue.	6. Failure to break adolescent ties (egocentricity).
	7. Sexual *maladjustment* with frigidity, unhappy marriage.

Amenorrhea which occurs early during the starvation is a uniform symptom and with return of adequate nutrition, the menses are re-established. One of my medical confreres reports that in Puerto Rico, where severe grades of malnutrition are seen, a cessation of the periods frequently accompanies it. In each one of the cases investigated, *absence of ovarian*

hormone is noted, indicating that a severe disturbance of hormonal physiology has taken place. This is of especial interest, for, even without any estrogenic stimulation, the ovarian activity seems to regenerate itself, with return of normal weight. It is likewise of special note that none of these patients showed menopausal symptoms which would indicate a primary lack of gonadotropic stimulus from the anterior pituitary rather than ovarian hormone absence. The unusual opportunity was presented in Case VIII for a histologic examination of a portion of the ovary removed during an appendectomy. This showed a normal ovary containing follicles without evidence of maturity, though the gross organ looked somewhat pale and shrunken. As actual atrophy of the gonads does not occur, the presumption is that for proper pituitary-ovarian activity, certain nutritive elements or vitamins are necessary.

The exceedingly *low basal metabolic rate,* without elevation of cholesterol, is indicative of another secondary effect. The lowest rates reported are in anorexia nervosa, though Turner's figures show that rates in Simmonds' disease are the same. Thyroid medication is not indicated because, with the re-establishment of normal nutrition and weight, the metabolic rate also returns to normal. Apparently we are dealing with a functional thyroid deficiency dependent upon nutritional and hormonal (anterior pituitary) deprivation.

In certain of these patients there has been a *glossy tongue* and a serious *gingivitis* and often marked *decay of the teeth,* necessitating complete removal in one case and partial removal in another. These conditions likewise must be related to a dietary (vitamin-calcium) deficiency. A *blue coloration to the sclera* is observed in many of the severe cases. This suggests somewhat the appearance seen in osteogenesis imperfecta. A frequent, unexpected condition seen in these patients is an overgrowth of hair on face, arms and legs. This *hypertrichosis* is in marked contrast to the falling of the hair, especially in the axilla and pubes, seen in true pituitary cachexia.

There is some evidence that starvation has an effect upon the anterior pituitary, causing impaired function with a secondary deficiency of the thyroid, gonads and adrenals—a pluriglandular insufficiency in which, however, there is no atrophy

occurring in the endocrine organs, as the few autopsied cases confirm. It is not difficult, then, to consider this functional pluriglandular disease as sharply differentiated from the true Simmonds' disease with its clinical and postmortem evidence of progressive lowering of glandular activity leading to endocrine atrophy and eventual death.

Psychoneurotic Manifestations.—Having placed the endocrine manifestations as entirely secondary, we must seek elsewhere for the etiologic factors in cachexia nervosa. A defect in diet, if it will produce such profound psychological changes and emaciation, must have behind it a very strong motivating force. This, according to the study of the patients recorded, has in each instance proved to be a serious mental conflict, resulting in a psychogenic disturbance of great intensity. The preponderant complaints of these patients are *gastro-intestinal.* They have fixed obsessions as to what all foods or certain ones will do to them. No persuasion will enlighten them. They say it will produce gas, or a tight feeling, or cramps, or pain, or the food feels as though it was not going through. There is obstinate constipation requiring all kinds of cathartic efforts, and nausea and a seasick feeling. Patients say avoidance of food made them feel better, and gives them more energy to do things. Associated with these were queer ideas about diets; each article of food was critically weighed and ruled out until there was practically nothing left to take, and food was hidden or surreptitiously disposed of. Feelings of *apprehension, anxiety, fear, desperation* and *hopeless depression* often accompanied the occurrence of the symptoms, and a continual urging of the patients to eat produced only a stiffer defense and a more thorough fixation of the symptoms in the intestinal tract. A true colitis, whether of the nervous type or otherwise, supervened in some cases and seemed further to increase the symptoms.

The most uniform single factor was a conflict between the patient and her parents. This *family fixation* was at times caused by close dependence upon or by a serious antagonism to the mother, with a marked admiration for the father (unresolved Oedipus situation), or by a violent inner conflict attempting to establish an independence from the parents who held the patient in subjugation. This would lead to aggres-

sive thoughts against the parents, a sense of guilt as a result, and recriminations resulting in a further withdrawal and escape almost to the point of suicide. *Failure to break adolescent ties* brought about a further sense of defeat and inferiority, compensation being gained by building up certain ego satisfactions. Those starting in the gastro-intestinal tract shunted the sexual into the oral and anal channels, thus further conditioning the vegetative level. It was noteworthy that in each case reported the patient had experienced *sexual maladjustment*. Frigidity was common, masturbation provided only moderate satisfaction, marriage was avoided until recovery, and if marriage had occurred, it was a source of further instigation of the illness on the basis of premarital maladjustments and an absence of any mature sex life with the husband. Why could not these young women grow up? Principally because they were not trained to and were not allowed to. Often the mother was at fault, maintaining her daughter as a child to satisfy her own selfish desires, the child turning to the father and perhaps being thwarted there also, and in despair giving up and escaping into illness.

TREATMENT

In order to bring about recovery it is necessary first to take the patient away from the parents—often a difficult feat. This is well accomplished in a hospital, when, and if possible, the patient should be isolated in a separate room. Then she must be shown by careful medical study and explanation that she has no organic disease, and lastly she must be given a certain quantity of food and a weight chart kept. Enlist her interest and cooperation in the procedure. Weighing must not be done too often and must always be done by a nurse. Placebos at first may be desirable, to avoid removing all medicinal props. A normal diet is given, and the patient must be shown that the symptoms are no better or no worse following the ingestion of one article or one quantity of food than following another. Adequate vitamins, minerals and fluids must, of course, be given.

But all of this is subject to variation and is only the scaffolding upon which to work, for the real therapy is *psychological*. The patient must understand thoroughly the father

and mother relationship. She must learn the nature of her own emotional drive toward sex, and toward the ego; and she must be taught to realize in what way she failed to meet the issues of life which brought about her illness, how her symptoms developed chronologically, and with what stimulus and emotional instability; and then, with full understanding, she will definitely have less reason to support her organic symptoms. In other words, psychotherapy of a thoughtful, careful, detailed and analytical nature is needed. Unless the psychological exploration is relatively deep, it will not be possible properly to readjust the patient and send her along with any real insight into her illness and herself.

CONCLUSIONS

1. Ten cases of severe emaciation are reported with recovery in all which were followed through.

2. The syndrome is called "cachexia nervosa" rather than the older term "anorexia nervosa," because anorexia is an incomplete and misleading term.

3. The clinical picture is that of starvation with cachexia, occasional dehydration, dry skin, gingivitis, and a striking blue color to the sclera. In addition there is an endocrine disturbance presenting amenorrhea, very low basal metabolic rate without increased cholesterol, hypertrichosis, and absence of follicular (estrogenic) hormone without genital atrophy.

4. This is not Simmonds' pituitary cachexia because it is not accompanied by atrophy of the endocrine glands or aging of the tissues, by falling out of hair, or by uniform fatality.

5. The remainder of the clinical syndrome shows a preponderance of gastro-intestinal symptoms with obsessions about food and a refusal of it, with indigestion and vomiting. Associated with this are feelings of anxiety and fear, and depression pointing toward suicide in certain cases. Also there are family antagonisms and fixations, with egocentricity and basic retention of the adolescent state, with failure to bring about psychological maturity. Sexual maladjustment is common, with infantile repression and marital unhappiness.

6. Treatment in severe cases requires hospitalization, a careful dietary regimen with adequate vitamins, and psychotherapeutic re-education. Endocrine therapy is of no value.

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RECENT DEVELOPMENTS IN THE TREATMENT OF EARLY SYPHILIS

IN the thirty years which have elapsed since the advent of arsphenamine a large number of drugs have been introduced into syphilis therapy. Most of these have been discarded, only a handful having withstood the test of time. Until recently the majority of cases of syphilis were treated with arsphenamine, neoarsphenamine or silver arsphenamine; a small number received sulfarsphenamine or bismarsen. There is no doubt that with the proper usage of these drugs early syphilis can be "cured" in the biological sense in some cases, and in the serological and clinical sense in a large number of cases. However, for a variety of reasons, chief among which is the incidence of toxic reactions, search for the ideal arsenical (or drug) has continued unremittingly. And, too, efforts have been made to devise simpler applications of these drugs so that equivalent therapeutic success might be achieved without burdening the patient with the necessity for continuing treatment relentlessly for one to two years.

In recent years a number of new drugs and new methods have been introduced into the armamentarium of syphilis therapy. It is my intention to discuss these briefly, chiefly from the viewpoint of early syphilis. Early syphilis offers the greatest opportunity for the control of infectiousness and thus the greatest hope for ultimate eradication of the disease. It is in this stage that we can aim fairly for prompt and complete destruction of all the parasites and, having accomplished this, eliminate every danger of late complications. Besides, the criteria for evaluation of therapeutic results are quite sharp in

early syphilis, and even though enough time may not have elapsed to give a final estimate of the value of new drugs or methods in the prevention of late visceral manifestations of syphilis, past experience will reasonably indicate the eventual outcome. We can certainly compare the toxicologic effects with those of the older and more accepted drugs and procedures.

ROUTINE METHODS OF TREATMENT

Before the results of the studies made by the Cooperative Clinical Group[1] were published, the treatment of syphilis was frequently haphazard, individualistic, or followed the technic outlined by Neisser. The findings of the Cooperative Clinical Group were so conclusive, and subsequent corroboration has been so plentiful, that none can doubt the importance of this contribution. Certainly the most effective routine treatment for early syphilis is the method advocated by this group, namely the *continuous alternating procedure* without any intervals of rest. Therapeutic success is distinctly higher by this method than by the *intermittent method* of Neisser, by irregular methods, or by the earlier so-called intensive methods. It may be well at this point to recall that the intermittent method (Neisser) consists of combined courses of an arsenical and heavy metal separated by rest periods of six weeks, during which no treatment is administered.

The comparative therapeutic success by these two routine modes of therapy in early syphilis, shows 79.7 per cent satisfactory results for the continuous method, and 65 per cent for the intermittent method.[2] It is obvious, then, that the preferable routine procedure is that outlined by the Cooperative Clinical Group, the unfortunate component being the need for treatment prolonged far beyond the endurance of a great mass of our population. In a recent survey, Russell[3] of the United States Public Health Service found that, of 6807 patients with early syphilis, only 16 per cent received adequate treatment, that is, at least 20 doses of an arsenical. He also investigated a series of 580 patients for evidences of progression of the disease. Of these, 328 received grossly inadequate treatment, with a resultant incidence of 16.9 per cent of neurosyphilis, and 3.4 per cent of cardiovascular syphilis; 191 patients received less than standard treatment, and 10.5 per cent con-

tracted neurosyphilis and 5.8 per cent cardiovascular syphilis. The remaining sixty-one patients in this group, all of whom were adequately treated, showed 1.6 per cent of neurosyphilis but no cardiovascular involvement.

Trisodarsen.—In the past five years, two new trivalent arsenicals have been applied in syphilis, mapharsen and trisodarsen. Trisodarsen (first presented as Triarsen) has not been extensively studied. It is a trivalent organic arsenical, containing not less than 19 per cent arsenic, and has the virtue of being neutral or slightly alkaline in solution, obviating the necessity for neutralization. In animals its chemotherapeutic index is 18, as compared with an index of 6 to 10 for neoarsphenamine.

Toxic Reactions and Therapeutic Results.—Stokes and Beerman[4] treated 189 patients with early syphilis with this drug, and stated that the incidence of minor reactions was about the same as with neoarsphenamine, but somewhat less than with mapharsen. The incidence of dermatitis was high, occurring in four patients of the series. In patients treated for six months or longer, there occurred 8.9 per cent of relapses, as compared with 19.7 per cent for a similar series studied by the Cooperative Clinical Group. Spinal fluid examinations at the sixth month showed 4.3 per cent positive, as compared with 8.2 per cent for mapharsen[5] and 18 per cent for neoarsphenamine[6] in other reported series.

The authors conclude that the drug meets the requirements of the Cooperative Clinical Group for the treatment of early syphilis; that its striking efficiency with reference to reversal of the serologic reaction of the blood and the prevention of asymptomatic neurosyphilis, and also its dermatitis-producing qualities require further study. This drug is still under clinical investigation, and is not recommended for general use.

Mapharsen.—Mapharsen (arsenoxide) was first synthesized by Ehrlich and Hata,[7] who called it amidophenolarsenoxide. They advised against its clinical use because of greater toxicity and lower chemotherapeutic index than arsphenamine. Arsenoxide can be converted into arsphenamine by reduction, and is in turn produced by the oxidation of arsphenamine. On the basis of experiments with animal trypanosomiasis, Voegtlin and Smith[8] in 1920 postulated the theory that the arsphen-

amines, when introduced into the body, had first to be converted to arsenoxide before a trypanocidal or spirocheticidal effect occurred. In 1932 Sanford Rosenthal[9] demonstrated, for the first time, the presence of arsenoxide in animal tissues after the injection of arsphenamine and neoarsphenamine. Tatum and Cooper[10] in 1932 stated that pure arsenoxide has a higher therapeutic index for rabbit syphilis than any other antisyphilitic agent.

Mapharsen is a stable chemical compound, of constant composition, containing 29 per cent arsenic; solutions do not become toxic on standing for several hours. The maximum dose, 0.06 gm., contains about 17 mg. of arsenic, while the equivalent dose of neoarsphenamine, 0.6 gm., contains about 120 mg. Since its introduction, a large literature has sprung up, almost all testifying to its diminished toxicity compared with the older arsenicals, and also to its therapeutic effectiveness.

Toxic Reactions and Therapeutic Results.—To quote from a study in which the present author collaborated,[11] of a series of 188 cases of early syphilis treated with mapharsen, by the continuous method recommended by the Cooperative Clinical Group, 84 per cent achieved a satisfactory result and 16 per cent were unsatisfactory. In a similar, fairly comparable series of 169 cases, treated with arsphenamine and neoarsphenamine, the Cooperative Clinical Group obtained satisfactory results in 79.3 per cent and unsatisfactory results in 20.7 per cent. While the difference in results is small and the cases of the Cooperative Clinical Group were observed over a slightly longer period of time, the indications are that mapharsen, used in the same manner as arsphenamine and neoarsphenamine, will yield at least an equivalent number of satisfactory results. In our series of 188 patients treated with mapharsen, three mild cases of jaundice occurred, the remaining disturbances being of a minor nature, such as nausea, vomiting, pain in the arm, headache, pruritus without eruption, and one "fixed" eruption. We concluded that the "results obtained with mapharsen in the treatment of early syphilis appear to be as satisfactory as those obtained with other effective arsenicals when the same method of therapy is used. The favorable results thus far obtained with mapharsen, especially in view of

its minimal toxicity, ease of preparation and administration, justify further trial on a more extensive scale, with careful prolonged observation."

The fact that nitritoid reactions do not occur with mapharsen has made its use in cardiovascular syphilis more frequent. However, its influence upon cardiovascular syphilis and neurosyphilis cannot yet be judged with finality, but it is reasonable to believe, from the published data, that it will have neither greater, nor lesser, effect than the arsphenamines. In Wassermann-fast syphilis[12] we found it neither more nor less effective than other arsenicals.

In syphilis complicating *pregnancy,* there is a divergence of opinion. Castallo and collaborators[13] treated 116 syphilitic pregnant women with mapharsen and bismuth, and concluded that this drug was less well-tolerated than neoarsphenamine, and gave results somewhat inferior to it. Astrachan,[14] who used mapharsen in twenty-four pregnant women, did not encounter a greater incidence of reactions, and stated that neoarsphenamine or mapharsen can be used with equal benefits in the treatment of syphilitic pregnant women.

INTENSIVE METHODS OF THERAPY

With arsphenamine as the weapon, Ehrlich envisioned the concept of *sterilisatio magna,* the complete sterilization of the host with a few concentrated doses of the spirocheticide. However, there arose the seemingly insurmountable wall of increased toxicity which spurred the search for a drug which would be intensely parasitotropic, but minimally organotropic. To the present this desideratum has not been attained. But, until this ideal drug is discovered, "perhaps by employing agents already at hand in a new form of attack it might be possible to exert greater effect on the disease."[15] Moore[16] has written: "It must be recognized that even given more clinics, better clinics and free clinics, the control of syphilis by present-day treatment methods is still far from satisfactory. Treatment is too prolonged, too painful, too dangerous, too expensive. Efforts of investigators to develop better and especially shorter methods of treatment should be encouraged."

In the past, so-called intensive, "sterilizing" systems of treatment were fostered, and pursued, until it became evident

that the therapeutic results were miserably poor in comparison with those obtained by routine, prolonged methods. In Germany, such systems were practiced by Scholtz[17] and Schreus,[18] and in our country by Pollitzer.[19] The Cooperative Clinical Group states that such intensive procedures (chiefly Pollitzer's) gave only 23.4 per cent satisfactory results in early syphilis.

Hyperpyrexia.—Attempts to accomplish the "cure" of early syphilis by hyperpyrexia alone have been generally unsuccessful, probably because it is impossible to elevate the temperature of all the body tissues to the thermal death point of the Spirochaeta pallida. The experience of Epstein and Cohen,[20] in thirty-one patients with early syphilis treated with hyperpyrexia alone, is revealing: three clinical recurrences occurred after cessation of treatment, and no case showed a reversal of the blood Wassermann to negative. Combined electropyrexia and chemotherapy has been tried, by Simpson and Kendell[21] with greater promise. These investigators treated twenty-eight patients with fifty hours of sustained fever (105°–106° F.), and six patients with twenty to thirty hours. The fever was induced at weekly intervals for ten weeks, and combined with it was given 10 injections of an arsenical; after cessation of the fever 20 more weekly arsenical injections were given. These patients were observed from one to slightly over four years. Of the thirty-four patients so treated, thirty-one became or remained negative, and three became less positive. All had spinal fluid examinations, which were negative. The entire therapeutic procedure required some thirty weeks for consummation.

Intravenous Drip with Neoarsphenamine.—In 1933, Chargin, Leifer and Hyman[22] treated twenty-five patients with early syphilis by an intensive method. The principle that the slow intravenous administration of toxic drugs diminished their toxicity, as proved by Hyman[23] and his collaborators, was applied in the administration of neoarsphenamine. The average dose given was 1 gm. daily for four consecutive days, a total dose of 4 gm. for the course. No further treatment was given.

Therapeutic Results.—A report of observations after five years[24] was made on fifteen patients in this series who could be

followed: twelve were completely satisfactory; one had suffered a reinfection after thirty-one months and could still be considered satisfactory; one had received some 20 mercury injections after leaving the hospital, and was entirely satisfactory after five years; the last patient had suffered either a relapse or a reinfection, but since the data to prove reinfection were incomplete, he alone had to be considered a failure.

In February, 1938, another series of investigations[25] was begun, again with neoarsphenamine in the same dosage. Eighty-six patients in all were treated. At the present time seventy-eight patients in this group can be evaluated: seventy-one are satisfactory (three of these seventy-one have suffered proved reinfections and can still be considered satisfactory); three are placed in a pending group, that is, at the time they were lost from observation their serologic tests had become almost but not completely negative; four patients are deemed irrevocable failures, three because of infectious relapse, and one because of sero-relapse. It should be noted that the serologic examinations performed in this study were of unusual thoroughness; the blood specimens were subjected to routine Wassermann, titered Wassermann, Kolmer, Kahn diagnostic, Kline exclusion and Kline diagnostic tests, these tests being performed simultaneously in three different laboratories, the United States Public Health Service (Dr. John F. Mahoney), the New York City Department of Health (Mr. John Koopman), and the laboratory of the hospital where the patient was being observed.

Spinal fluid examinations were made on thirteen of the original fifteen (1933 series) and sixty-seven of the seventy-eight in the second (1938) series—all were negative. These were performed six months or more after treatment and in some instances repeated after two to five years.

Intravenous Drip with Mapharsen.—In October, 1938, treatment with neoarsphenamine was discontinued; from then until June, 1940, a series of 275 patients were treated by the intravenous drip procedure with mapharsen,[26] in the hope of reducing toxicity. The initial total dose was 0.4 gm. mapharsen, given in a period of six days—this was quickly elevated, by 100 mg. increments, until the maximum dose of 1.2 gm. in five days was being given. I have intentionally omitted a dis-

cussion of the technic used with neoarsphenamine, since we believe mapharsen the drug of choice.

Technic.—Briefly, the technic with mapharsen is as follows: a No. 20, 1½-inch needle is inserted into a vein of the forearm in the morning, and left in situ for a period of ten to twelve hours. Use of a forearm vein obviates the need for an arm board and restriction of movement. During this period a total dose of 0.24 gm. mapharsen dissolved in 2400 cc. of 5 per cent dextrose is allowed to flow in. In the evening the needle is removed, and the patient is permitted out of bed. This procedure is repeated on five consecutive days, making the total dose for the course 1.2 gm. mapharsen. No special preparations for treatment are made; the diet is the usual solid one, fortified by additional carbohydrates.

Therapeutic Results.—In evaluating the results obtained with mapharsen we must realize that the longest observation period has been two years, and the shortest four months. Naturally the figures to be cited can serve to indicate only a trend, and cannot at the present time be considered final. For purposes of study we divided the 275 patients into two groups: Group A, 157 patients, who received doses from 0.4 gm. to 1 gm. mapharsen (obviously many of these patients received

TABLE I

GROUP A (SMALL DOSE), 140 PATIENTS

Outcome	With 1 Course of Therapy	With 4 Pts. Classed as Reinfections	With 2 Courses of Therapy
Failure.....	24* (17%)	20 (14%)	11 (7.8%)
Pending.....	5 (4%)	5 (4%)	8 (5.7%)
Satisfactory.....	111 (79%)	115 (82%)	121 (86.5%)

* Four patients are considered reinfections, hence satisfactory. Ninety-three spinal fluid examinations: all negative.

grossly inadequate doses), and Group B, 118 patients, all of whom received 1.2 gm. mapharsen.

Of the 157 patients in Group A (Table I), seventeen were lost from observation before the tenth week after discharge from the hospital, leaving 140 patients who can be evaluated.

After one course of massive dosage, there were twenty-four therapeutic failures: ten were Wassermann-fast, three developed a serologic relapse and eleven had infectious relapse. Of the eleven patients with infectious relapse, we believe there is excellent evidence to show that four actually suffered reinfection, and must therefore be considered satisfactory. The five pending patients have almost, but not completely, cleared serologically.

Of the twenty-four patients called therapeutic failures, fifteen were subsequently re-treated by the intravenous drip procedure with larger doses of mapharsen. Ten of these fifteen re-treated patients have become satisfactory.

TABLE II

GROUP B (LARGE DOSE), 105 PATIENTS

Outcome	With 1 Course of Therapy	With 3 Pts. Classed as Reinfections	With 2 Courses of Therapy
Failure.....	5* (4.8%)	2 (1.9%)	1 (0.95%)
Pending..... ...	17 (16.2%)	17 (16.2%)	18 (17.15%)
Satisfactory.....	83 (79.0%)	86 (81.9%)	86 (81.9%)

*Three patients may be considered reinfections (satisfactory). Thirty-six spinal fluid examinations: all, but 1, negative.

In this series of 140 patients, ninety-three have already had spinal fluid examinations, all with negative findings.

Of the 118 patients in Group B (Table II), thirteen were lost from observation before the tenth week after discharge from the hospital, leaving 105 patients available for evaluation. After one course of massive dosage, there were five therapeutic failures, all patients with infectious relapse. However, of these five patients, we believe three are indubitable cases of reinfection, not relapse, and hence satisfactory. There are seventeen patients whose serologic reversal is as yet incomplete (observation period too short) and who are then classed as pending.

Of the five patients called therapeutic failures, four were retreated with the same dose (1.2 gm.) of mapharsen, and three of these are already satisfactory, the fourth still pending.

In this group of 105 patients, thirty-six have had spinal fluid examinations. All were negative, except one which was made less than six months after therapy; this fluid must be rechecked before final decision is possible.

An analysis of the therapeutic failures (including the seven patients we believe reinfections), after one course of massive dose arsenotherapy, reveals twenty-four patients in the small dose group, and five patients in the large dose group. Of these twenty-nine patients, twenty had had their infection over eight weeks, and nine less than eight weeks. It is suggestive that the seven patients we deem reinfections all fell

TABLE III

COMPARISON OF TOXIC EFFECTS IN NEOARSPHENAMINE AND MAPHARSEN SERIES

Toxic Effects	Neoarsphenamine (111 Treatment Courses)	Mapharsen (294 Treatment Courses)
1. Primary fevers	69 (62%)	119 (40%)
2. Secondary fevers	71 (64%)	39 (13%)
3. Toxicodermas	50 (45%)	35 (12%)
4. Dermatitis exfoliativa	1* (0.9%)	0
5. Blood dyscrasias	0	0
6. Renal damage	0	0
7. Jaundice	4 (3.6%)	2 (0.7%)
8. Peripheral neuritis	39 (35%)	5 (1.7%) mild
9. Cerebral symptoms (total)	2 (1.8%)	3 (1.02%)
(*a*) Hemorrhagic encephalitis	1 (0.9%)	1 (0.34%)
(*b*) Single convulsion	1 (0.9%)	1 (0.34%)
(*c*) Disorientation	0	1 (0.34%)
10. Fatality	1	0

* Received sulfanilamide for a complicating gonorrhea.

into the group who had had their infection less than eight weeks. After two courses of massive dosage (given to nineteen of the twenty-nine failures), there remain at the present time twelve irrevocable failures, or approximately 5 per cent of the 245 patients observed. Of the remainder, approximately 10 per cent are still pending, and eighty-five per cent are up to now satisfactory.

Comparison of Toxic Effects in Neoarsphenamine and Mapharsen Series.—Examination of Table III reveals clearly the lower incidence of reactions of all sorts with mapharsen than with neoarsphenamine.

Primary fever occurred the first day of treatment, lasted six to twelve hours and subsided spontaneously. Continuation of treatment was almost always possible the next morning. This fever is of minor importance and is of the nature of a Herxheimer reaction. *Secondary fever* came on after termination of the treatment course, lasted from one and one-half to four days, and was usually, but not always associated with a toxicoderma.

Toxicodermas, in the majority of instances, appeared on the seventh day, that is two days after the termination of treatment, and were preceded by and accompanied with secondary fever. They were practically always morbilliform in type, more rarely urticarial, and are probably identical with the so-called erythema of the ninth day of Milian. The eruption does not sensitize the patient to the arsenicals, since several patients took this drug subsequently without cutaneous reaction. The eruption is a benign one and should in no way be identified or confused with true arsenical exfoliative dermatitis.

Dermatitis exfoliativa was observed in only one patient. It occurred in a patient in the neoarsphenamine series, the eruption appearing some six weeks after arsenotherapy, in the course of treatment of an acute gonorrheal urethritis with large doses of sulfanilamide. Complete recovery took place.

No *blood dyscrasias* or evidences of *renal damage* were observed, despite careful blood counts (including platelet counts) before and after therapy, and daily urine examinations. There was never elevation of the blood urea nitrogen, and concentration tests showed no impairment of renal function.

In the neoarsphenamine group four patients developed *jaundice,* in the mapharsen group two. In all cases the jaundice was comparatively mild and cleared with unusual rapidity. No patient developed any evidence of atrophy of the liver. In a percentage of the patients some temporary elevation of the icteric index, without clinical jaundice, was observed.

Peripheral neuritis, affecting the sensory nerves of the lower extremities chiefly, was seen in thirty-nine patients in the neoarsphenamine series, and in five patients in the mapharsen series. Attempts to prevent this complication, by ad-

ministering large doses of thiamin chloride during treatment, were unsuccessful. It is undoubtedly produced by the arsenic, the average quantity being 800 mg. with neoarsphenamine and 348 mg. with the largest doses of mapharsen used; this would account for the extremely low incidence of this complication with the latter drug. All patients with this condition recovered spontaneously in from two to six months.

Cerebral complications occurred in two patients in the neoarsphenamine series. One patient developed the characteristic syndrome of hemorrhagic encephalitis to which he succumbed. This was the only fatality in the entire series of 386 patients who received drip treatment. Another patient had a single convulsive seizure, on the sixth day; the spasm lasted about two minutes, and was followed by prompt, spontaneous and complete recovery. In the mapharsen group three patients had cerebral complications: one had typical hemorrhagic encephalitis, another a single convulsive seizure, and the third a period of disorientation and mental confusion without convulsions. All recovered completely.

Comparison of Toxic Effects with Those from Routine Treatment.—Comparison of the toxic phenomena with those observed in routine treatment is not easy. It must be remembered that our patients were all in bed in the hospital and under careful scrutiny. Stokes[27] states that "probably the only true reaction statistics are to be obtained from a bed service with patients under constant and long-time control." It is very likely that in ambulatory treatment many reactions occur which are never observed or reported to the physician. Insofar as serious reactions are concerned, we had one fatality in 386 patients. In recorded series the incidence of deaths from arsenicals varies from 1 in 200 to 1 in 1000 patients. Cole[28] reported twelve arsenical deaths in 1212 patients. "Hemorrhagic encephalitis stands out as the leading cause of death and because it is so largely idiosyncratic in onset, probably the most unavoidable cause," according to Stokes.[29] Such complications as aplastic anemia, acute yellow atrophy of the liver and crustaceous dermatitis, which are often fatal in outcome, were not observed by us. The annoying peripheral neuritis seen in the neoarsphenamine series has been prac-

tically entirely eliminated by the use of mapharsen. All the other reactions which we have reported are of a minor nature.

CONCLUSIONS

In conclusion, it may be said that early syphilis can certainly be "cured" by the routine procedure advocated by the Cooperative Clinical Group; that approximately equivalent therapeutic success but with less toxicity may be obtained with mapharsen as with arsphenamine and neoarsphenamine. The great drawback is the prolonged time needed to achieve satisfactory results, and the inability to induce patients to continue treatment for this required time. Combined chemotherapy and electropyrexia seems an effective procedure, but it, too, requires thirty weeks for completion. The intravenous drip procedure, in a five-day treatment period, apparently yields results equal to, if not better than, optimal routine measures. However, we feel that this procedure is not yet ready for general usage; that it should be investigated further in carefully controlled treatment centers; that every effort be made to eliminate, as far as this is possible, treatment hazards. But we feel strongly that rapid sterilizing therapy, of one form or another, is the sine qua non of syphilis control, in view of the difficulty of maintaining patients with early infectious syphilis under routine treatment for an adequate period of time.

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FROM THE MEDICAL CLINIC OF THE PRESBYTERIAN HOSPITAL AND THE DEPARTMENT OF MEDICINE, COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY

SYPHILIS OF THE HEART

THIS discussion of syphilis of the heart will be limited to a description of the clinical effects of specific involvement of the coronary arteries and of the heart muscle.

SYPHILIS OF THE CORONARY ARTERIES

Syphilitic disease of the coronary arteries manifests itself in two ways: (1) obstruction to the coronary blood flow by stenosis or occlusion of the orifices of the coronary arteries, and (2) syphilitic involvement of branches distal to the orifices. The role of syphilis in producing lesions of the latter type is questionable. Medical opinion is at variance on this point, but all of the available evidence points to the fact that syphilis of the coronary arteries distal to their orifices is an uncommon lesion and is of doubtful clinical importance. In contrast to this, however, *syphilis of the coronary ostia* is generally acknowledged to be of great importance in influencing the course and prognosis of cases of syphilitic aortitis.

Pathogenesis.—Inasmuch as the coronary arteries arise from the base of the aorta, syphilitic involvement of their openings implies the pre-existence of luetic aortitis. As the syphilitic process usually stops at the upper level of the sinus of Valsalva, except for penetration along the attachments of the valves, an abnormally high point of origin of the coronaries is an important factor in the involvement of their orifices. It is also well recognized that in about 90 per cent of all cases of syphilitic involvement of the coronary orifices, *aortic insufficiency* is present; consequently, a consideration of luetic coronary orifice involvement resolves itself into a discussion

of aortic insufficiency with and without this complication. It may be stated, parenthetically, that a diagnosis of syphilitic occlusion of the coronary arteries in the absence of signs of aortic insufficiency is hazardous and quitely likely to be wrong. Contrary to the general impression, angina does occur in patients with syphilitic aortic insufficiency without the presence of narrowed coronary ostia, so that the clinical differentiation between cases with involvement of the coronary orifices and those without such involvement is often difficult or impossible.

In most forms of obliterative endarteritis of vessels the size of the coronaries, occlusion depends upon the formation of a thrombus which subsequently undergoes organization. In closure of the coronary arteries due to syphilis, however, the process develops in that part of the coronary vessels which lies within the aortic wall. An obliterative endarteritis occurs in the vasa vasorum which penetrates the muscular wall of the coronary arteries, with consequent impairment of the blood supply. A progressive increase of the subendothelial layer of the coronary wall takes place, which narrows the lumen of the coronary vessels until total occlusion may result. The endothelial lining of the coronary lumen is preserved intact, so that thrombosis does not occur. Interference with the efficiency of the coronary blood flow becomes marked, but the process is so gradual that a collateral circulation may be developed. The gradual closure also explains the comparative immunity of the patient from symptoms and the remarkable freedom of the myocardium from scarring, even though the coronary circulation is impaired. These pathologic considerations explain to some extent the difficulty in the clinical detection of this complication.

A clinical and pathologic study has been made on a series of cases of syphilitic aortic insufficiency with and without stenosed coronary orifices.[1] No major differences were observed between the two groups as regards symptoms, physical findings or other diagnostic criteria. It was shown, however, that there is one group of cases with narrowed coronary ostia which could be identified by reason of certain distinctive clinical and pathologic features.

Symptoms.—*Pain* is the predominant symptom of which these patients complain. It is usually severe and is localized

to the chest with or without radiation to the shoulders, arms or epigastrium. It is paroxysmal in type, is usually precipitated by exertion or emotional excitement and is relieved by rest. The pain is a symptom of coronary insufficiency. Because of the role of arteriosclerosis in the production of the same type of pain, the diagnosis of syphilitic closure of the coronary orifices should be limited to relatively young people in the third and fourth decades of life who show evidence of syphilitic involvement of the aortic valve.

Physical Signs.—The physical findings are those of syphilitic aortic insufficiency. The heart in these cases of syphilitic closure of coronary orifices, however, is usually not enlarged. It is possible that interference with the blood flow through the coronary arteries diminishes the ability of the heart to enlarge. A *diastolic murmur* is usually heard at the base of the heart, particularly in the third interspace just to the left of the sternum. The *pulse* may be collapsing in type. The blood *Wassermann test* is usually positive. In this particular group of cases, congestive failure does not occur, death supervening before the appearance of myocardial insufficiency. The electrocardiogram and *x*-ray studies are of no aid in differentiating syphilitic aortic insufficiency with or without luetic closure of the coronary ostia.

Antiluetic treatment is usually of no avail in this type of case, although bismuth, mercury and iodides should be used. Arsenicals are to be avoided.

The *prognosis* is poor. Patients rarely survive three months after the onset of pain. Death usually occurs suddenly.

Course.—The following case history offers a typical illustration of the course and manner of death in an instance of this type:

CASE I.—M. S., a thirty-three-year-old Negro housewife, was admitted to the Presbyterian Hospital because of acute pain in the epigastrium radiating to both shoulders, both arms and the precordium. She had been perfectly well until five years before, when she married. Almost immediately, she developed "womb trouble," with pain in the abdomen and leukorrhea. Three weeks before admission, after climbing three flights of stairs she suddenly developed terrific substernal pain which radiated through to the back and to both shoulders and arms. The pain was so severe that she fainted. Since then she had had recurring attacks of similar pain while walking, eating, or on drinking cold water. With these severe attacks of pain she would break out into a cold sweat and feel faint for a few minutes.

On *examination* the patient appeared acutely ill, crying out at intervals and holding her hand to the precordial region. The examination was negative except for the cardiovascular system. The heart was slightly enlarged. The rhythm was regular and the rate was 80 per minute. The heart sounds were of poor muscular quality. A short systolic murmur and a long blowing diastolic murmur were heard at the base and in the third left interspace, transmitted over the precordium. The pulse was of the collapsing type. The peripheral vessels were not sclerotic and the blood pressure was 172/50 mm. Hg in both arms. The liver was not palpable, the lungs were clear, and there was no edema of the extremities. The white blood count showed 6000 cells, with 53 per cent polymorphonuclears. A blood Wassermann was not done. The temperature was 99.3° F.

While under observation the patient had attacks of severe pain coming on every few minutes. Nitroglycerin gave only momentary relief. Morphine was more effective but the pain persisted. Twelve hours after admission she suddenly stopped breathing.

At *autopsy*, the pathologic findings of interest were confined to the heart and aorta. The heart weighed 400 gm. The epicardium was smooth and glistening. The pulmonic, tricuspid and mitral valves were normal. The aortic valves were thickened and retracted, and their commissures were widened. The root of the aorta, for a distance of 2 cm. above the commissure, was thickened, irregularly wrinkled and contained many shallow pits and depressions. This process at the base of the aorta ended abruptly in a wavy line. In the remainder of the aorta, the intima contained many small elevated gray and yellow patches, most marked in the thoracic aorta. The mouths of the coronaries were markedly involved. The right coronary had two pin-point orifices and the mouth of the left coronary was practically completely occluded. The distal portions of both coronaries were normally patent and contained only a few atheromatous plaques. The myocardium was red, firm and free of obvious fibrosis or infarction. This was confirmed by microscopic examination and the smaller vessels were found to be normal.

This patient illustrates in a typical way the course of events in that form of luetic coronary orifice involvement which may well be called the *acute* form of the disease. The process in the coronary ostia evidently advanced so rapidly that, clinically, the patient showed many of the signs and symptoms of acute coronary obstruction. This condition is observed particularly when both coronary ostia are affected by the luetic process. It is only in this type of case that the diagnosis of syphilitic involvement of the coronary orifices can be made with any degree of accuracy.

SYPHILIS OF THE MYOCARDIUM

Diffuse interstitial fibrosis of the myocardium is not uncommon in congenital syphilis. In acquired syphilis, however, lesions of the myocardium are rare in relation to the frequency of the infection.

Gummata.—As in syphilitic involvement of the coronary arteries, there is division of opinion in the medical literature as to the types of luetic involvement of the heart muscle. On one point there is general agreement. Gummata of the heart, while rare, constitute an accepted pathologic lesion. Clinically, they may give rise to no symptoms, while on the other hand sudden and unexpected death has been attributed to them. Gummata of the heart can be recognized clinically only when they occur in the conduction system, particularly in the bundle of His. Interference with this tissue induces heart block of varying degrees of severity, which not infrequently results in the appearance of the Adams-Stokes syndrome.

Diagnosis.—The diagnosis of gummata of the heart muscle is to be suspected in the sudden appearance of this symptom complex in an individual in the third to fifth decades of life, who has had no previous cardiac history and whose blood Wassermann reaction is positive. The following case history illustrates these criteria:

Case II.—H. W., a forty-one-year-old Negro truck driver, was admitted because of increasing dyspnea on exertion and dizzy spells of three weeks' duration. The past history was negative for rheumatism or heart trouble of any kind. Fourteen years earlier he had contracted a chancre and had received no antiluetic therapy. Three weeks before admission, he had had a transient dizzy spell while at work. This had recurred on several occasions and ten days before admission he had become momentarily unconscious. He had noticed the appearance of mild dyspnea on exertion for two weeks, but he complained of no precordial pain, edema or nocturnal dyspnea.

Physical *examination* showed that he could lie flat in bed without distress. The pupils reacted sluggishly to light. The heart was normal in size, with a rate of 72 per minute. (The rate had been noted to be 30 per minute by a competent observer twenty-four hours before.) There was a soft systolic murmur at the apex but no diastolic murmur was heard. The blood pressure was normal. Both the blood and spinal fluid were positive for syphilis by the Wassermann test. The x-ray and fluoroscopic examinations of the heart, made during a period of complete heart block, showed slight enlargement of the heart but no evidence of aortitis. The electrocardiogram showed sinus rhythm with prolonged conduction (P–R 0.27 seconds) and bundle branch block.

For *treatment* the patient was given potassium iodide by mouth and bismuth intramuscularly. Four days after the first dose of bismuth, complete heart block appeared. Antiluetic therapy without the use of arsenic was given daily. This consisted of the continued administration by mouth of 3 gm. of potassium iodide and the intramuscular injection of bismuth or mercury at weekly intervals. He received, in all, only eleven injections—six of bismuth and five of mercury. After six months' treatment, the heart block had disappeared. During this interval, infrequent attacks of unconsciousness recurred,

in one of which asystole was present for over two minutes. Intracardiac injection of adrenalin was effective in restoring the ventricular rhythm.

With the restoration of sinus rhythm, the patient was able to resume his work as a truck driver. After a period of observation lasting over six years he is enjoying excellent health, working hard and is completely free of cardiac symptoms. With continued antiluetic therapy, the blood Wassermann has become negative. The electrocardiogram shows sinus rhythm with prolonged conduction (P–R 0.24 seconds). The bundle branch block noted in the first electrocardiogram has persisted throughout the period of observation.

Several points are of interest in this case. The diagnosis of a luetic lesion in the interventricular septum was made on the basis of the conduction defects as noted clinically and confirmed by the electrocardiogram. The existence of gummata in the heart muscle without clinical evidence of aortitis is noteworthy. It is probable that, in this case at least, the gumma was anatomically very near the bundle of His. Pressure exerted on the bundle of His by the gumma was apparently responsible for nutritional disturbances in this tissue. Damage, so caused, was sufficient to precipitate complete heart block for a period of six months. That the bundle was not directly and completely involved by the luetic process is proved by the fact that normal rhythm was restored. If this were not true, the scar formation caused by absorption of the gumma would have resulted in permanent complete heart block.

Interstitial Myocardial Fibrosis.—The other type of involvement of the heart muscle which has been ascribed to syphilis is the lesion described as interstitial myocardial fibrosis, with perivascular round cell infiltration.

The possibility that acquired syphilis produces this picture of interstitial myocardial fibrosis is very questionable. This type of case is being included here because of the belief held by a few observers that such a relationship does exist and a clinical picture has been drawn.[2] Certainly these cases are very rare and the clinical characteristics ascribed to them are common to other cases with enlarged hearts which possess similar definitive clinical and pathological features. It is to be emphasized, therefore, that while the clinical picture is clear-cut, it is the opinion of most workers in this field, including those in this Hospital, that the etiology of this group is still in doubt.[8]

Clinical Picture.—Hitherto these cases have been included in that group of patients with large hearts with congestive failure in whom none of the usual causes for heart disease are to be found, either clinically or pathologically. This group has been termed, variously, chronic myocarditis, fibrous myocarditis, and idiopathic hypertrophy of the heart. The clinical picture is quite distinct. These cases of interstitial myocardial fibrosis are seen in relatively young people in the third and fourth decades of life, and occur most commonly in the Negro race. They are characterized by the complete absence in the history of congenital heart murmurs, rheumatic fever, scarlet fever, frequent sore throats and any other type of infection which has been associated with the production of heart muscle damage. There is no history of hypertension. In other words, none of the usual causes of heart disease are present. The symptoms which bring them to the doctor are those of congestive heart failure, *i.e.*, dyspnea, orthopnea and anasarca. There is no history of cardiac pain.

On *examination,* the degree of heart failure is found to be severe. The heart is tremendous in size, and frequently with gallop rhythm. There are no murmurs and blood pressure is usually within normal limits. The diastolic blood pressure may be slightly elevated during the period of heart failure, but, with return of compensation, the blood pressure is found to be well within the normal range. There is marked edema, usually with free fluid in the pleura and peritoneum. The venous pressure is markedly elevated. The electrocardiogram shows normal sinus rhythm, with or without evidence of heart muscle damage as reflected by deviation of the T waves. There are usually no auriculoventricular conduction defects, and rarely bundle branch block is present. The blood proteins are normal. The blood Wassermann is usually positive.

Treatment and Course.—Treatment of the heart failure with the usual methods—*i.e.*, bed rest, limitation of fluids and salt, digitalis in adequate amounts, and the use of diuretics—is rewarded with rapid and almost miraculous recovery of compensation and the complete disappearance of symptoms. The heart, however, remains markedly enlarged, with little or no diminution in size despite the remarkable clinical improvement. Freedom of symptoms does not continue for long.

Within six months, the patient reappears with exactly the same clinical picture which characterized his first appearance, and again compensation is regained but with somewhat less facility than on the first occasion. This process is repeated again and again—each time the period of compensation is shorter, the time spent in regaining compensation longer. After anywhere from three to six bouts of heart failure, and within two to three years after the first onset of symptoms, the patient dies in congestive failure. Throughout the entire period the heart remains enormously enlarged, and there is complete absence of evidence concerning the etiology of its hypertrophy.

At *autopsy,* the heart is much larger and heavier than normal. All of the valves are competent and the coronary arteries show little or no sclerosis from their orifices to the smallest branches. The heart muscle grossly gives no evidence of infarction and there are no large scars. Microscopically, however, there is a marked and extensive interstitial fibrosis, with the muscle fibers showing individual hypertrophy but isolated and surrounded by a network of fine scarring. There is usually some round cell infiltration in the perivascular areas of greater or lesser degree, depending upon the stage of the activity of the process.

Antiluetic therapy does not appear to influence the course of this type of heart disease. This is understandable when it is remembered that it is the extensive scar formation with consequent impairment of nutrition of the remaining heart muscle that is the cause of loss of compensation. Treatment is best directed toward decreasing as much as possible the patient's activity so as to conserve the cardiac reserve which he still possesses. The continuance of digitalis, limitation of fluids and a diet poor in salt are all helpful to this end.

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THE TREATMENT OF ADDISON'S DISEASE WITH DESOXYCORTICOSTERONE ACETATE

THE synthetic preparation of desoxycorticosterone acetate has made a potent cortico-adrenal hormone available for the first time to the usual patient with Addison's disease. Heretofore, patients have had to rely upon simple salt replacement therapy reenforced to a certain extent by injections of cortical extract. These extracts, although helpful when given in large quantities during crises, have been too expensive for routine daily use; and the effects of salt therapy alone, while considerable, have been in a number of cases far short of optimum. It can be fairly stated that with desoxycorticosterone acetate it is now possible in a majority of cases to obtain a very satisfactory control of the disturbance of salt and water metabolism which by and large dominates the clinical picture of Addison's disease.

DIAGNOSIS OF ADDISON'S DISEASE

Clinical Considerations.—Patients with Addison's disease are characterized by an *increased pigmentation, asthenia* and *low blood pressure*. The nature and cause of the pigmentation is not understood. Typically it is a dirty brownish discoloration involving chiefly the face and hands, genitals and flexor creases. It may be accompanied by bluish-brown "ink spots" in the buccal mucosa. In some cases it is not marked, in others it may be represented by a dyspigmentation resembling vitiligo.

Asthenia is usually the chief complaint. It may be quite severe, insidious in onset, and accompanied by a moderate weight loss. Hot weather is poorly tolerated; slight colds and intestinal upsets are unusually prostrating and are frequently accompanied by unexplained high fevers. These minor illnesses may develop into *major adrenal crises* with complete gastric intolerance, delirium, coma, and the entire picture of "medical shock": cold cyanotic extremities, contracted veins, low blood pressure and almost imperceptible pulse. The effect of administering sodium chloride and fluids to such patients is almost diagnostically dramatic. Similarly, the reappearance of symptoms following brief withdrawal of sodium from the diet remains one of the best clinical methods for establishing the diagnosis.

Laboratory Tests.—*Estimation of Serum Sodium Concentration.*—There are a few laboratory tests which are of considerable help in the diagnosis and control of these patients. Chief among them is the estimation of serum sodium concentration. When it is not possible to carry out this test directly, the serum sodium concentration can be calculated conveniently from the serum chloride and serum bicarbonate concentrations by the formula: serum chloride concentration in milli-equivalents per liter plus serum bicarbonate content in milli-equivalents per liter plus 10 equals the milli-equivalents of sodium per liter. Values below 135 in the absence of an appreciably increased nonprotein nitrogen concentration are suggestive of Addison's disease provided the low chloride and carbon dioxide determinations are not obviously explainable on the basis of vomiting, diarrhea or severe sweating.

Provocative Test.—If the patient is first seen during a major illness with all these complications present, diagnosis will have to rest upon a general evaluation of the clinical and laboratory data. Later, when the patient has been restored by the administration of fluid, salt, glucose and cortical hormone, the diagnosis can be established by observing the effect of salt withdrawal upon the symptoms and serum sodium concentration.

If, as a result of a few days' withdrawal of salt from the diet, an otherwise fairly normal patient has a reappearance of the symptoms of Addison's disease with a falling blood pres-

sure and a drop of several milli-equivalents in serum sodium concentration, the probabilities are that he has Addison's disease. Since this provocative test is not without danger, it should be carried out cautiously and in a hospital.

Other Tests.—Other laboratory tests of some help in this condition are those for the *nonprotein nitrogen concentration,* which is frequently elevated during crises; the *blood sugar concentration,* which tends to be low in the fasting state and may be associated with a flat glucose tolerance curve; and the *serum protein concentration,* which along with the body weight may be taken as an index of the state of hydration of the patient once a baseline has been established.

In general, it is a good plan to watch the blood sugar concentration as well as the blood sodium concentration rather closely during major adrenal upsets, since, particularly after glucose infusions, there may develop a severe hypoglycemia quite uncorrelated with the salt and water balance and clinically rather difficult to recognize amidst the welter of other symptoms.

THERAPY WITH DESOXYCORTICOSTERONE ACETATE

The cortico-adrenal hormones in general may be divided into two main groups: those having an oxygen attached to the eleventh carbon atom and affecting carbohydrate as well as salt and water metabolism, and those lacking this oxygen atom and apparently affecting only salt and water metabolism. Desoxycorticosterone, as the name implies, falls into this latter group and in doses of the order of 5 mg. a day produces in human subjects a very considerable decrease in the excretion of sodium, chloride and water, and a moderate increase in the excretion of potassium. Since the usual patient with Addison's disease suffers predominantly from the effects of excessive sodium loss, the ability of this new hormone to regulate sodium excretion makes it a most welcome addition to the therapy of adrenal insufficiency. It does not, however, have significant direct action upon carbohydrate metabolism and consequently should not be considered a complete replacement therapy. Moreover, since amounts greater than those required for the maintenance of normal sodium balance may cause serious complications, it should not be used carelessly or indiscriminately.

Dosage.—The question of how much desoxycorticosterone acetate to give a patient depends upon the patient and the particular clinical circumstances. A few patients do very well on salt therapy alone and for them the routine use of hormone is probably unnecessary. With other patients, the liberal administration of sodium chloride, 10 to 20 gm. a day by mouth, does not seem productive of results as good as those which can be obtained with the hormone and a normal sodium chloride intake. In this group, daily subcutaneous injections of desoxycorticosterone acetate in oil or the implantation of pellets in amounts sufficient to furnish 1 to 10 mg. of hormone daily are usually sufficient to bring the serum sodium concentration to normal and maintain it at that level. This stabilization of serum sodium concentration is usually attended by marked clinical improvement, increase in strength, increase in appetite, and increase in weight.

Once equilibrium is established the patient, in most instances, can be discharged to continue his treatment at home. He should be cautioned, however, that unusual gains in weight, particularly if associated with dependent edema and shortness of breath, are probably indicative of congestive heart failure as a result of overdosage with hormone. Similarly, he should be told that in hot weather or during intercurrent illnesses his requirement of hormone may be appreciably increased and that under such changing circumstances he may need the aid of his physician in adjusting his dosage. This adjustment can usually be accomplished without difficulty by following the blood pressure, water balance, weight, serum protein and serum sodium concentrations and controlling the intake of hormone, fluid and salt in such a manner as to prevent the patient from either bogging down with edema or drying up with adrenal insufficiency.

Treatment of Major Adrenal Crises.—Major adrenal crises require both an intensification of therapy and a sharpening of laboratory and clinical control. Adequate amounts of hormone, saline, glucose, cortical extract, and if necessary blood transfusion, must be given as soon as possible to bring the patient out of shock; but since dehydrated, severely ill Addisonian patients pass very easily into congestive heart failure, this treatment must be applied with care in order to avoid

sudden large increments of blood volume which place too great a strain upon a presumably inadequate myocardium. By and large, therapy may consist of an immediate divided intramuscular injection of 25 mg. of desoxycorticosterone acetate in oil, subcutaneous injection of 25 cc. of a potent aqueous cortical extract, and a slow infusion of 1500 cc. of 5 per cent glucose in normal saline to which has been added another 25 cc. of aqueous cortical extract. Subsequent therapy will depend entirely upon the patient's condition and an evaluation of the laboratory data. The probabilities are that approximately two thirds of the initial treatment will have to be repeated on the following day; and if the serum protein concentration has fallen to an edema level without evidence of congestive heart failure, increased venous pressure or cardiac silhouette, a serum transfusion may be desirable at that time to help in maintaining the circulating blood volume.

COMPLICATIONS OF DESOXYCORTICOSTERONE ACETATE THERAPY

If one accepts the congestive heart failures as being due to obvious overdosage with hormone and salt, and the hypoglycemic reactions as being intercurrent phenomena which appear whether the hormone is used or not, the complications of desoxycorticosterone acetate therapy about which we know anything are, at present, relatively minor. *Hypertension* has not been severe and has been confined to older patients where a moderate incidence might be expected when the adrenal insufficiency is well compensated. *Gynecomastia* and *menstrual disturbances* have not increased in frequency; and although the hormone is closely related to the sex hormones in chemical structure, rather extensive animal experiments have failed to demonstrate that it has significant depressant action upon either the gonads or the pituitary. However, it does seem that deaths in desoxycorticosterone acetate treated patients have been much more frequent among female patients than among male patients and this aspect of the problem requires further investigation.

In some of the cases overtreated with hormone there has been a suggestion that part of the patient's collapse may have been associated with an *unusual excretion of potassium*, suf-

ficiently extensive to lower the serum and muscle potassium concentrations to a level incompatible with normal neuromuscular function. Although the possibility of this complication can be easily demonstrated in experimental animals, it is unlikely that it will occur to any extent in a well controlled and carefully watched patient.

SUMMARY

In general it may be said that desoxycorticosterone acetate has done, to a certain extent, for Addison's disease what insulin has done for diabetes. It has not cured the disease but it has made it possible to control what is clinically the outstanding physiologic disturbance, namely, an excessive renal excretion of sodium.

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RECENT ADVANCES IN RADIATION THERAPY

A TRULY mighty metamorphosis has taken place in radiation therapy since its first employment beginning at the close of the last century. Replacing the crude, hand-evacuated Crookes cathode tube capable of sustaining only a small amount of electrical energy, we now have the recently developed *x*-ray tube of a million volt capacity. In place of the minute quantity of radium originally produced by the Curies, there is now the large quantity radium pack, meticulously measured and standardized, its effects accurately calculated and determined before actual use in operative procedures.

The evolution of the *x*-ray apparatus from Crookes to Coolidge, with due credit to the work of Snook, Waite and others, has kept pace with the development of the art and science of *x*-ray therapy. Indeed, it might well be said that the constant progress in the science of radiology was in great measure aided by the cooperative interest of the manufacturer and the radiologist in devising machines to meet advancing medical needs.

So, too, was it with radium, for it was the early producers of radium who increasingly promoted the use of this miraculous agent for healing.

It is worth pausing at this stage in the career of the young science of Radiation Therapy to note what developments have occurred, what foundations have been laid, and how firm is the structure that now so proudly stands. Within these forty-five years several phases have been passed, not unlike those through

which many of our fundamental sciences have had to go before emerging as a basic science.

THE ERA OF DISCOVERY

The chemical and physical properties of *x-rays* were recognized soon after their discovery by Röntgen in 1896, but its biological properties were not discovered until the harmful results of its radio-activity on the skin had been noted by the early workers in this field. The therapeutic use of *x*-rays was recognized through observing the epilating effect of these rays, and the reddening of the skin resulting from their use for diagnostic purposes. In the early days, *x*-ray diagnosis called for long exposures, and Daniel in the United States and Marcuse in Germany were the first to note the baldness following *x*-ray exposure, in the examination of the skull for fracture. In 1897 Freund in Vienna, with this effect in mind, empirically treated a case of hairy nevus on the skin of a child with good results.

Radium, too, ever since its discovery by the Curies, has played an important role in therapeusis. Radium therapy began with the recognition of its biological effect on the skin, Pierre Curie being the first to note a rather painful skin reaction following the experimental attachment of a radium plaque to his forearm. It was, however, Becquerel's burn which called serious attention to the possibilities of radium as a therapeutic agent.

In 1901 Becquerel received from the Curies some of the first radium they had made and he carried it for several days in his vest pocket. Later, when he noticed a persistent erythema on the skin adjacent to this pocket, and consulted his friend Bessier, a dermatologist, the latter recognized in this radium reaction a similarity to the dermatitis exhibited by the early workers with *x*-rays. Cognizant of the action of *x*-rays on the skin, Bessier suggested that Becquerel loan the radium to the renowned St. Louis Hospital in Paris, which was then the center of dermatologic therapy in France. Wickham's work in the early days of radium therapy, mostly on superficial lesions, gave indications of a large field of usefulness. As with *x*-rays, radium came to be employed for all sorts of lesions,

with varying results, and it was not until recently that a more rational therapy was developed and established as the standard of treatment we have today.

The report of Freund's success served to stimulate the use of *x*-ray in medicine and resulted in the creation of the science of *x*-ray therapy. While at first only dermatologic conditions were treated by irradiation, since then many other lesions throughout the body have been treated. In 1901, Pfahler reported the cure of surface *epithelioma* with *x*-ray and about the same time, Williams, another pioneer in this work, successfully treated epithelioma of the eyelids with *x*-rays, thus replacing mutilating surgery.

At the outset, only surface lesions were treated, but not long afterward *x*-rays came to be utilized as a panacea for virtually all types of diseases and naturally, since adverse results were inevitable, this therapy soon came into disrepute. Gradually, however, the limitations of its therapeutic value were realized and a more correct rationale for its use was employed. Although the effect on glandular structures was not then clearly understood, its possibilities for affecting toxic conditions were early suggested. When Williams and Pfahler succeeded in treating toxic thyroid cases with this medium, they did much to advance it to its present position as essential in the treatment of hyperglandular and hypoglandular conditions.

In the beginning, our ability to treat human beings by *x*-ray therapy was restricted by various handicaps—lack of sufficiently powerful apparatus, unstable *x*-ray tubes, limitations in voltage and filtration, and uneconomic methods of administration. Indeed, treatment with the older forms of apparatus constituted quite an ordeal, for it was necessary for the patient to lie in position on the treatment table for uncomfortably long periods of time. Today much more effective treatment is administered in a mere fraction of the time formerly required, because with the improvement in design and in materials used, higher voltages are made possible, thereby increasing the intensity of the *x*-rays and reducing considerably the time of administration. The pressing problems then were to create and employ harder *x*-ray tubes, better filtration, and increased number of treatment portals, together with increases in the

amount of dosages administered and increased frequency of treatments.

The promiscuous use of *x*-ray and radium resulted in no little damage by reason of overexposure to the rays on the part of the physician, technician and the patient, because it was not then realized that *distance* and *filter*, which we now know play so important a part in radiation, were prime factors in protection. Pfahler was one of the first to recognize the effects of *x*-ray absorption in the skin; he interposed a filter between the tube and the patient, thereby enabling a more penetrating dose to be given to the underlying structures without adversely affecting the superficial tissues. The important factor in the treatment of deep-seated lesions was the question of the distance of the *x*-ray tube from the patient. In the early days of roentgen therapy the tube was placed close to or directly on the skin. Williams, in 1903, suggested placing the tube at a distance from the body, thus giving a more intense dose to the deeper structures. This subsequently became one of the leading principles in radiation therapy.

Because of the caustic effects of *x*-rays, they were promptly seized upon as a means of treatment for all types of lesions, but the persistent applications led to gross injuries of the skin. Meanwhile, however, some fundamental researches were being carried out, and as a result, a more scientific basis for radiation therapy was gradually established, eliminating skin damage.

The newer apparatus also enables us better to utilize our knowledge of the physics of radiation, thereby directing effective and intensive irradiation internally. Until quite recently no definite physical *measurement of dosage* existed and of course the time-honored method of trial and error left very much to be desired. Establishment of a definite International Standard of measurement of dosage—the so-called "r" unit—has provided us with a safe control medium for prescribing therapeutic irradiation. By means of this unit and with suitable apparatus for its measurement it is now possible to transfer a given technic from one hospital to another. Moreover, the ray quality has been more or less standardized, and it is possible now to determine and denote more uniformly the penetrability of radiation. A number of measuring instru-

ments are available today that facilitate obtaining a continuous reading of the intensity applied.

THE ERA OF STABILIZATION

This marks the next step in the development of radiation therapy. Originally, procedures were based upon hit-or-miss principles, the early treatment of cancer in the United States being by these purely empirical methods. Grubbe was probably the first in this country to treat breast cancer by irradiation. During the World War in 1914 there was a temporary lull in the scientific development of *x*-ray therapeusis. In 1918 Kronig and Friedrich in Germany published the result of their very painstaking researches in the physics and biology of radiation. This work, which established a more scientific basis for irradiation than had existed hitherto, marked a turning point in the science. Through their studies of ionization by x-rays these scientists worked out the factors necessary for safe and efficient "deep therapy," establishing the limits of biologic action of *x*-rays and setting what they called the erythema, cancer and ovarian sterilization dose.

There was, at this time, a distinct tendency to use *shorter* x-rays, in an effort to approximate the short gamma rays of radium. By the use of filters the more or less complex *x*-ray beam was made more homogeneous. Regaud believed such a ray exerted a greater selective action upon cells and that the x-ray and gamma rays were selective for nuclear chromatin of the cells upon which the hereditary factors depend. The rays suppress or suspend cellular reproduction within the tissues. It was his opinion that each variety of neoplasm corresponds to a definite position in the scale of radiosensitivity. The aim of treatment, then, was to administer a lethal dose to the tumor cells and fall short of the destruction dosage for normal tissue cells. Ewing, too, stated that various tissues behave toward radiation in differing manner which may be affected by previous structural changes and other pathologic conditions. The first principle of proper radiotherapy was the recognition of the variation in *tumor sensitivity* to radiation: Proper irradiation requires that all parts of the tumor receive equal and sufficient amounts of radiation, as far as possible simultaneously, and within a relatively short period of time.

Tumors generally have been classified according to their histologic structure, and while there have been classifications from the standpoint of radiosensitivity, no positive criterion has as yet been devised for establishing the radiocurability of pathologic tissue. Broder's classification of tumors has been accepted as a well-defined outline on which to base an understanding of the reaction of tissues to radiation.

Because skin lesions require radiation of low penetrative power, Bucky devised the *Grenz rays* which he suggested would affect the superficial tissues and leave unharmed the adjacent ones. The Grenz ray of long wavelength, almost that of ultraviolet, is of value in numerous superficial conditions.

Seeking to create conditions with *x*-rays similar to those obtained with radium contact therapy created the necessity for devising a means of applying *x*-rays of low depth dose and a high dosage rate to superficial or accessible neoplasms. This led Chaoul to develop the method of *contact x-ray therapy* in which the *x*-ray tube itself is placed in direct contact with the surface of the neoplasm and many thousand roentgens are administered through a light filter to the tumors. Contact therapy is limited in scope and as yet it has not replaced radium for the treatment of superficial neoplasms. Owing to the low penetrative power of this form of therapy it is too soon to judge whether or not the healing of malignant lesions is permanent when it is used.

As the physics of radiation developed and the factors of filtration, distance and portal size were better understood, it was possible to produce, by increasing the voltage of the generator, a newer, homogeneous, penetrating ray approaching the gamma rays in wavelength, thus affording a more effective method for treatment of deeper-lying lesions. One of the important aids in the development of the *x*-rays was the invention of the *Coolidge x-ray tube*, without which it would not have been possible to utilize the higher processed *x*-rays. This new tube permitted a better employment of the physical standards of radiation and by saving time in treatment saved both patient and apparatus. In time it led to the development of the *super-voltage x-rays* of 400,000 and 1,000,000 volt capacity. Considerable new data have been accumulated regarding supervoltage *x*-ray therapy, but it is not yet pos-

sible to state definitely that such high voltage gives superior results. It is stated that supervoltage x-ray therapy permits the safe administration of a larger dose with diminished back scatter, thus delivering a significantly high tumor dose. However, as yet there is no conclusive evidence of the superiority of supervoltage x-rays.

The question of the *rate of administration* of irradiation has recently come to the forefront. In 1920 Seitz and Wintz, working clinically along similar lines, set standards for dosage which they called the carcinoma, sarcoma and sterilization doses. At that time the practice, first established by the Germans, was to deliver an intense radiation at one sitting, and not infrequently patients were unable to endure such therapy. Proceeding from the principles elaborated by Dessauer for irradiating patients homogeneously by using several converging beams, there was proposed the *crossfire method* which permitted treating a lesion more uniformly from several portals. In this way there was avoided excessive dosage with possible subsequent deleterious sequelae at the site of intensive treatment when given through one portal, and furthermore, it permitted the administration of a larger dose to the tumor without damage to the skin and underlying tissues. Solomon, in France, later established the *divided dose method* which permitted treatment from several portals per day by dividing the amount of dosage into equal parts each day, thus enabling a larger total dosage to be given, in an amount which was not safely possible were all the treatment administered at one time. Subsequently, Pfahler in this country developed the *saturation method* of treatment by which a prolonged amount of therapy could be administered over a long period of time by repeated dosages, always less, however, than a total dose administered on separate days.

In the new method of divided dose treatments the time factor or rate of application of the x-rays plays a much greater part than heretofore. Coutard promulgated the method of *slowly administered protracted irradiation in gradually increased amounts,* thereby avoiding the deleterious effects on normal tissues which had been occurring with the older method of rapidly administered intensive dosages given at one sitting.

The clinical employment of *radium* was influenced by the

penetrative character of the beta and gamma rays given off, the convenience with which radium could be used for treatment of surface and cavitary lesions, and the readiness with which it could be employed for intratumoral treatment.

In the early days, treatment, just as with *x*-rays, was by the method of trial and error. All kinds of devices, applicators of every shape and type, were employed to administer the radium, but little consideration was given to the factors of safety, filtration and distance. Radium varnish plaques were quite the vogue. The frequent occurrence, however, of injuries following radium therapy led to a halt in its use, and until a better understanding of its physical and biological effects was developed, adverse results continued.

Not long after the discovery of radium it was found to give off a gas or emanation called *radon* which had the therapeutic characteristics of radium itself, except permanency. The early applicators which utilized this gas provided unfiltered radiation that was caustic and destructive in character. The cystoscope, which was invented about 1878 in Vienna, permitted the development of intrabladder radium therapy with *radon seeds*. In 1914 Duane discovered that radon could be piped into small glass tubes whereby tissue could be irradiated both intramurally and superficially. Dominici, working with radium, noted that a more far-reaching effect could be produced by so filtering the radiations as to absorb all but the gamma rays. Janeway, realizing the value of these findings, began to use *radon tubules* (glass seeds) in cancer therapy.

In 1917, Barringer, employing these emanation seeds as suggested by Duane and Janeway, established the method of *interstitial irradiation* through the operating cystoscope in the treatment of bladder and prostate tumors. To avoid the caustic effect produced by bare seeds, Fialla, in 1924, suggested making them from gold tubing instead of glass, thereby providing a filter for the radon which gave better results. Today radium applications, whether by seeds, needles or tubes, are made in most instances with filtering devices.

When larger amounts of radium became available, efforts were made to substitute for the *x*-ray a large pack of radium for administering radiation therapy through the surface from a distance. It has been found that *radium beam* or *radium pack*

therapy is as efficient as any other method of radiation in the treatment of lesions within the effective range of radiation. The effective range depends to a large extent on the quantity of radium available.

That there is a sound basis for considering *preoperative irradiation* of value was enunciated some time ago by Regaud who claimed that it diminishes the risk resulting from surgically disseminated cancer cells, that it can be more effectively carried out in tissues not cicatrized by operation, and that when properly given it does not interfere with subsequent surgical operative procedures. Today preoperative irradiation is an established procedure in many clinics. Although this is a field of irradiation that offers promising potentialities, it has not as yet superseded curative *x*-ray therapy, especially in the treatment of gynecologic conditions where *x*-ray and radium in smaller quantities constitute the most effective remedies.

THE PRESENT ERA OF ESTABLISHED RADIATION THERAPY

In 1904 Halberstaedter, proceeding along the lines of research suggested by Albers Schonberg, Bergonie and Tribondeau on the biological effect of radiant energy on human tissues, noted the sensitivity of ovarian tissues to *x*-rays and the selectivity of these rays on such tissues. Based upon their studies of the biological action of *x*-ray on human tissues, *Bergonie and Tribondeau* formulated the *law*, named after them, that: "Inactive cells and cells in an active state of mitosis are more sensitive to the radiation than are cells which have already acquired their adult morphologic and physiological characters." It was their convincing studies which gave determined impetus to a better understanding of the biological effects of irradiation and stimulated further advances in roentgen therapy, leading to the establishment of today's exact clinical methods of treatment. Unquestionably the possibilities envisioned for irradiation in connection with gynecology gave this form of therapy its greatest stimulus and served to put it on a par with the older tried and tested surgical methods of treatment currently in use.

It was in 1903 that Morton in New York first reported the treatment of *fibroids* by *x*-ray sterilization. Today, not only is this treatment well established as most effective and advis-

able, but irradiation has replaced surgery in many gynecologic conditions.

Because of the sensitivity of the hematopoietic system to irradiation, irradiation was early suggested for the treatment of *leukemias*. The success attending the cases tried in those early days led to the continued use of this modality. Later Heublein recommended the method of spray or whole body irradiation for this disease and this appeared to give better results. At the present time a measure of success has been achieved by Laurence et al. from the injection of radioactive phosphorus, produced with the cyclotron, into the blood stream; this seems to give a more lasting therapeutic effect in controlling leukemia. It is too soon to say whether this method of therapy is better than repeated irradiations with *x*-ray.

The generally recognized radiosensitivity of *lymphoblastoma* has made irradiation the method of choice for its treatment. Experience, however, has shown that, while in most instances this type of neoplasm is sensitive, much greater dosages over a longer period of time are required to achieve good results than have hitherto been employed for this condition.

In *mouth and throat lesions* the evolution of the protracted radiation method has made radiation the therapy of choice. The discovery of an endocrine method of diagnosis has greatly influenced the method of treatment in *gonadotropic neoplasms*. Today irradiation guided by these tests has proved to be a better method than heretofore in the treatment of such neoplasms. Even the untoward effects of irradiation have now been put to constructive use. From the outset it had been noted that following irradiation there was *growth restraint* on cells and in some instances there were malformations of limbs. Accordingly, in order to balance a deformity in one limb, the growth epiphyseal area of the normal limb is treated by irradiation to halt its growth. Obviously, this opens up a vast valuable field, especially in poliomyelitis cases.

Today, therefore, with the fundamental facts of radiation from both the physical and biological standpoints recognized and understood, this therapy is playing an important role in the treatment of benign and malignant conditions.

Clinical experience has made it possible to classify condi-

tions along the lines of radiation therapeusis. In many *malignant conditions* irradiation is the treatment of choice. The more sensitive the tumor, the more readily responsive it is to irradiation; thus *embryonal tumors* such as seminoma of the testes, Wilms' tumors and ovarian embryonal tumors are best treated by irradiation. In *tumors of reticulo-endothelial origin* irradiation is the only effective method of control. Among such conditions are lymphoblastomas, Hodgkin's disease, lymphosarcomas, leukemias, thymic tumors and Ewing's endothelioma. Irradiation also is the treatment of choice in lesions of the mouth, tongue, lip and most skin conditions. It is the best treatment for cancer of the cervix and of the larynx and is the treatment of choice in carcinoma of the vagina and anus. In prostate, uterus, bladder, thyroid and salivary gland tumors it is as effective as surgery.

Bone lesions, especially Ewing's tumor, have been successfully treated by irradiation and in the control of such tumors and osteitis fibrosa cystica, this is the method of choice. In the latter condition irradiation works through its effect on the parathyroids.

Radiation is a necessary adjunct to surgery in the treatment of cancer of the breast, vulva, penis, secondary metastatic lymphadenopathy and parotid tumors. It is gratifyingly palliative in many carcinomatous conditions, especially in bone metastases.

In the field of *benign conditions,* irradiation is effective and often the method of choice in numerous conditions of inflammatory origin, such as acne, carbuncles, eczema, dermatophytoses, gas bacillus infections, arthritis and so on, and in the case of benign tumor growths such as fibroids and hypertrophic glandular developments. In various types of *endocrine disturbances*, both hypoglandular and hyperglandular in character, such as thyroid toxicosis and pituitary, parathyroid and ovarian dyscrasias, it is of real value. It is exceptionally effective in amenorrhea and sterility due to hormone disturbances.

That radiation therapy should be valuable in *neurologic conditions* was predicated upon the observation of Werner that analgesia followed radiography of injured persons. In 1904 Brauth advised *x*-ray therapy for the treatment of *epilepsy*, basing his opinion on the supposed stimulant effect of *x*-ray on

metabolism. Raymond in 1905 reported on the good results of *x*-ray in the treatment of syringomyelia and Williams found *x*-ray to be of value in the treatment of *herpes zoster*. Treatment of *intracranial tumors* was first suggested by Beclere who successfully employed *x*-ray therapy in the control of pituitary tumors. Progress in the science of radiation therapy brought with it a better understanding of the effects of *x*-ray and radium on body tissues and more and more neurologic conditions have come to be submitted to this form of therapy. The resistance of normal nerve tissues to irradiation has made possible the more intensive treatment of lesions associated with the nervous system.

THE FUTURE OF RADIATION THERAPY

Today a newer phase in radiation has appeared, viz., the *cyclotron* and the production of *artificial* radioactive elements and of *neutrons* capable of affecting human tissues. This nuclear physics is still, however, in its early stages and clinical results thus far known too uncertain to make evaluation of this therapeusis possible; we can only look forward expectantly and hopefully to this new venture. Although at present *x*-ray and radium are most effectively employed supplementary to one another, the million volt *x*-ray machine alone or the radium bomb alone may perhaps in the future become the ultimate in radiation curability value.

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CLINIC OF DR. RICHARD KOVACS

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RECENT ADVANCES IN PHYSICAL THERAPY

A CLEARER appreciation of the physical therapy field as a whole has been the result of the present-day, large-scale, clinical employment and of painstaking research. Physicians are learning to select methods and forms of physical treatment on the basis of the physiologic principles of action instead of relying on certain makes or types of apparatus. The tendency is definitely towards simplified devices. Many of the developments in recent years, especially those in heat therapy, relate to the same basic physiologic and clinical effects, but are better adapted to certain anatomic locations or pathologic changes.

THERMOTHERAPY

For the safe and efficient heating of the lower parts of the extremities, wrists, hands, ankles and feet, more extensive use is being made of conductive forms of heating. The *whirlpool bath*, consisting of water at a temperature of 105° to 110° F. which is kept whirling in a small tank by its own pressure or by a motor, combines gentle friction with sustained heat and also allows active exercise under water, especially in recent traumatic and arthritic conditions with swelling and limitation of motion. The *paraffin bath* employs melted paraffin at a temperature from 110° to 125° F., preferably controlled thermostatically; it is more useful in chronic traumatic and arthritic conditions.

SHORT WAVE DIATHERMY

The original spectacular claims for specific bactericidal and antiphlogistic effects and for selective heating of this new

method have not been corroborated by competent investigators. Short wave diathermy has, however, found its place as a convenient and fairly safe agent for deep tissue heating, offering the new technics of air-spaced electrodes and of coil heating or *inductothermy*. The latter technic is especially adaptable to the heating of an extremity or the body in toto and has become the most frequently used method for electropyrexia. A definite drawback of the technic of short wave diathermy, as employed up to the present time, has been the lack of dosage guidance, except that given by the patient's sensory response. Efforts have been made to construct dosimeters which will estimate dosage in the same manner as the milliammeter in long wave diathermy, but so far these meters have not been generally accepted for practical use.

Recent investigators have endeavored to compare the results of short and long wave diathermy in traumatic, gynecologic and arthritic cases, but so far the findings are more suggestive than conclusive. The contention that short wave diathermy is preferable in *acute* cases, whereas long wave diathermy is more efficient in *chronic* cases, can be sustained by the fact that the air-spaced technic of the new method as a rule results only in mild heating, which is well tolerated and beneficial in most acute cases. Long wave diathermy with the contact-plate method produces usually more intense heating which is better suited to chronic cases. It is quite problematical whether early experimental findings indicating that heating by short wave diathermy is more intense in the depth have any practical clinical meaning, because in actual practice the heating effect depends on a number of factors. I have found *coil field heating* convenient in peripheral vascular conditions on account of the easy controllability of the gentle and diffuse heating effect and the avoidance of skin contact; it is also efficient for treating two knees simultaneously.

Purulent infection of the skin, furuncles, carbuncles, paronychia, dental abscesses and lung abscesses have been enumerated by Schliephake and his followers as conditions in which short wave diathermy, especially of the shorter wave lengths, affords striking relief of pain and speedy resolution. Clinicians with seasoned experience emphasize on the other hand that mild heating is sedative in all suppurative processes

and that in all acute conditions there exists a natural tendency for fairly quick recovery. I have reported for many years that in localized skin infection, exposure to luminous heat from a simple heat lamp, repeated several times a day, gives very marked relief and satisfactory resolution. The late Elkin P. Cumberbatch achieved similar results with carefully applied long wave diathermy. Schliephake himself advises only mild doses of short wave diathermy. Hence, definite proof of the alleged specificity of short wave diathermy in these conditions can be brought about only by comparative observation on a large series of controlled cases—and no such series has as yet been reported.

In the light of present knowledge, there appear to be no specific conditions in which short wave diathermy is definitely preferable to long wave diathermy because of different clinical effects. Because of convenience of application, as already stated, its methods may be preferable in certain locations or conditions.

There are now certain conclusions possible regarding the advantages of long wave diathermy over the newer method. Short wave diathermy, as usually applied with large-size electrodes or an inductance coil, spreads its lines of force over all adjacent structures and wastes a good deal of energy. This is a drawback in treating heat-sensitive patients and in applying heat to such locations as the head or the neck where unnecessary heating of nonaffected parts is to be avoided. Long wave diathermy appears definitely preferable in treating accessible muscles and bursae, many of the joints and the cervical spine, because it allows better localized heating.

A *direct-contact plate method* in short wave diathermy[1] has been satisfactorily employed in our clinic for two years. It includes a tube apparatus with an additional patient's circuit, in which suitable extra condensers and coupling allow energy transfer through contact electrodes. While it necessitates the return to carefully applied contact metal electrodes, this method offers three other very definite practical advantages: 1. It enables the insertion of a milliampere meter in the patient's circuit for direct reading of the output of the apparatus and a fairly accurate estimate of dosage. 2. It enables handling

of the treatment cables without drawing energy from them, as they no longer form part of the treatment circuit; it also obviates the danger of a conflagration due to their overheating by crossing over each other or touching grounded metal. 3. Finally, it cuts down radio interference to a minimum because there is no superfluous scattering of energy into space. We now give preference to this method in treating most of the bursae and joints as well as body cavities and their contents; for example, the pelvic contents.

FEVER THERAPY

With fever therapy the center of much interest in recent years, the methods of its administration and all possible complications have been carefully studied. Various methods of fever therapy can produce equally good results in competent hands, but the preference is generally towards cabinets in which the induction of heating is done by short wave diathermy and the temperature of the cabinet is maintained by suitable radiant heating or air-conditioning. In competent and careful hands, both of the physician selecting and supervising fever cases and the technician administering the treatment, no serious accidents are likely to happen. The personnel still remains the most important part of any therapeutic procedure.

Clinical experience during the past few years has developed two ranges of therapeutic fever, *mild* and *severe*. Mild fevers from 103° to 105° F. are maintained for three to six hours and may be employed in syphilis and its various sequelae, in chorea, in multiple sclerosis, and in selected forms of arthritis and rheumatoid conditions. Severe fevers from 105° to 107° F. are maintained for from five to seven hours or longer and are employed chiefly in gonorrhea and its complications.

Since its advent, sulfanilamide therapy has come to be preferred in the treatment of gonorrhea; however, in view of a percentage of failure even with adequate sulfanilamide therapy, fever therapy will undoubtedly continue to be an important therapeutic adjunct in certain of the more resistant cases.

ELECTROTHERAPY

Galvanic Current.—The galvanic current, which is the basic current in electrotherapy, has greatly increased in use

in recent years, both as a tissue alterant and in the form of *electrophoresis,* for the carrying of medicinal substances into the skin. It has been shown anew that such electrophoretic introduction of foreign substances into the skin is followed by diffusion, adsorption and precipitation; also, that effects on deeper tissues are possible with drugs controlling pathways between the skin and internal structures. Extensive work has been done with vasodilating drugs, such as *histamine* and the choline derivatives, notably *mecholyl.* Favorable clinical results are being reported with both of these drugs in vascular spasm and fibrositis, neuritis, joint exudates in traumatic and rheumatoid arthritis, also in skin ulcerations. Histamine exerts a more intensive reaction and must be used for short applications only; it is generally preferred in applications to muscles; mecholyl requires more prolonged application and may exert systemic effects. Copper ionization has been favorably reported in fungous infections of the hands and feet.[1] The recent literature brings favorable reports on the relief of migraine and headache by histamine ionization,[2] of severe asthma by epinephrine ionization,[3] of arthritic pain by mecholyl and histamine ionization,[4] of muscular spasm by aconitine ionization[5] and of keloids and scleroderma by iodine ionization.[6]

Low Frequency Currents.—Low frequency currents for muscle and nerve stimulation have found a promising extension of their employment. A method of inducing *convulsions* by means of an alternating electric current applied to the brain was proposed by the Italians, Cerletti and Bini, in 1937 and was further developed by British psychiatrists.[7, 8] It aims to replace the more hazardous drug administration for "shock therapy" of mental disorders. This evolution is similar to the transition from the more hazardous malaria therapy to artificial fever therapy by physical means and is another proof that research workers have learned to consider physical agents alongside medicinal ones. Reports of its use are now beginning to appear in the American literature.[9, 10]

Ultraviolet Irradiation.—Small and relatively inexpensive units for local ultraviolet therapy have been recently introduced and have undergone extensive clinical and laboratory testing. The *thin window lamp*[11] is a mercury glow lamp emitting about 55 per cent short ultraviolet radiation, around

2537 angstroms, and some 35 per cent infrared radiation. This lamp is employed for local treatment only and can be applied in close contact to the skin up to ten minutes without causing blistering. Our clinical experience as well as that of others has shown the effectiveness of such radiation in pyogenic infections, fungous and parasitic affections of the skin, and sluggish ulcers and wounds. The relief of pain in minor infections and some ulcers after one or two treatments is often striking. The additional advantage of this application in skin infections such as impetigo is the avoidance of messy ointments.

The air-cooled *Kromayer lamp* furnishes a radiation similar to the standard mercury vapor lamp and obviates the cumbersomeness of the water-cooling arrangement. It is efficient for treating superficial areas on contact and cavities with the aid of suitable quartz rods.

UNDERWATER EXERCISES

Underwater exercises are finding increasing employment not only in infantile and spastic paralyses, but also in chronic arthritic and traumatic conditions. The partial elimination of gravity allows exercise of the weak muscles to a much larger extent; in nonparalytic cases the relaxing heat of the water helps to overcome stiffness. Such exercises can be given in the simple T-shaped device known as the *Hubbard tank,* which allows full extension of all four extremities; in its elaborations turbines and pumps whirl the water and quickly change its temperature. Large therapeutic pools are being built with special facilities for exercising and with motor equipment to hoist patients in and out.

The question of installation must depend primarily on the number of patients actually in need of such treatment, and on the availability of skilled technical personnel. Poor or inadequate muscle training in a tank or pool is inferior to adequate training by such simple means as moving a weak limb on a smooth well powdered board or swinging it freely from a sling attached to an overhead frame.

COMMENT

With the ever increasing number of new devices for physical treatment, the seasoned advice of such bodies as the Coun-

cil on Physical Therapy of the American Medical Association and of physicians specially qualified in physical therapy is indispensable before the usually enthusiastically broadcast claims for each new development are accepted. The chief problem of present-day physical methods is their more general and more rational employment in the various departments of medicine. There are all too many patients who would be potentially benefited by the early and efficient use of certain well proved physical treatments in addition to their other care, who because of lack of information or indifference do not receive such treatment. Patient cooperation and more widespread education about physical therapy offer the only solution of this problem.

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THE RELATION OF THE CLINICAL LABORATORIES TO THE PRACTICING PHYSICIAN

THE progress of medicine in all its branches is intimately associated with progress in the various medical laboratories. Each year sees new methods of study of disease. Each year brings a clearer understanding of the clinical value of older technics. As a direct result of this progress, our understanding of the mechanism of certain diseases is advancing, our abilities in accurate diagnosis are improving, and our capacities in prognosis are enlarging.

With this increased use of and dependence upon the results of laboratory procedures, the practice of medicine is also being threatened and it is important and wise for us to view these threats with some concern. In this brief introduction I should like to emphasize the clinical hazards of too much dependence upon the laboratory and to try to outline how far we can trust some of these procedures in the practice of our profession.

The Physician Must Know the Inherent Limitations of Ordered Tests.—There are certain generalities that should be discussed before considering the various specific laboratory methods. It is most important to remember that no laboratory examination should be pushed beyond its inherent limits of accuracy. Each test has certain limitations and it is essential that these should be fully appreciated. An an example: Not many years ago it was customary to calculate and report the degree of gastric juice acidity to several decimal points when the method itself is only able to record whether acid is absent

or present in large, normal or low concentrations. As another example, we might mention a recent decision of a large State hospital for the insane to make blood iodine determinations on their patients suspected of thyroid disease because they had noticed that the results of basal metabolic rate determinations were so inaccurate! The group that made that decision had not been informed that reports on blood iodine levels were only of value, first, when the technician had received prolonged and specialized training; second, when blank determinations were run after each test to insure the accuracy of the reagents; and third, when iodine vapor (even the opening of a bottle of the tincture of iodine anywhere in the ward during the preceding hour) was rigidly excluded from the atmosphere.

It is not the duty of the technician to question the clinical advisability of laboratory tests or to attempt to correlate the result of the procedure with the patient's clinical condition. It is the duty of the physician in charge to keep himself informed concerning the inherent limitations of the tests he orders and to be able to view the results obtained with discretion and clinical understanding.

Test Results Cannot Always Be Accepted at Face Value.—A second generality is one that is even more common and even more serious. I refer to the tendency of physicians to accept the results of laboratory tests at their face value, without question, even when that particular result does not fit in with the rest of the clinical picture. As we progress in our knowledge of medicine, it is becoming more and more apparent that at certain times and under certain circumstances laboratory procedures that are otherwise dependable become altered, yielding results that can result in serious errors. Numerous examples might be cited. A few of the more recent, personally observed, should suffice.

First, during the summer an elderly man died with what was clinically extensive carcinomatosis. His symptoms and physical signs suggested that the carcinoma might well be present in the lung, but six *x*-ray pictures taken over a period of two months showed nothing in the lung fields except a slight fuzziness in both lower lobes consistent with a moderate amount of "congestion." Autopsy revealed two enormous tumors as large as grapefruits, one in each lower lobe. A review of the *x*-rays

showed that these tumors were not visible even after their presence was known.

A second example is the relationship of the *sedimentation rate* to the degree of activity in *rheumatic fever*. There seems to be no doubt that as the rheumatic process increases in its severity, the sedimentation rate rises until a certain point is reached when, for reasons quite unknown, the sedimentation rate suddenly returns to normal. Why fulminating rheumatic fever that is rapidly progressing to a fatal termination should be associated with a sedimentation rate of less than 2 mm. in one hour is not known, but we do know that it occurs as part of this picture. Similar findings seem to occur in tuberculosis—the miliary form being often associated with very low rates.

Third, a young man without any symptoms suggesting purpura had a blood *vitamin C* level determination on his peripheral blood taken to act as a control for clinical study. By the best available methods, no vitamin C could be detected on that determination or on two subsequent determinations. The patient's capillary resistance was normal, his platelet level was normal. There was no suggestion of vitamin deficiency in the background and we must accept the fact that this method was inaccurate under the particular circumstances at that particular time.

One of the most intriguing parts of laboratory medicine is concerned with this question of the sudden, unexpected collapse of some of our most dependable tests. Study of the occasional instance of this sort may often reveal the opening of a door to a better and more detailed understanding of the physical and chemical bases for the behavior of a laboratory test, and each instance of this sort is a challenge to further thought and work.

The Professional Capacity of the Laboratory Worker.—The third point that we are far too apt to forget is the personal and professional capacities of the individuals doing these tests. I am not in any way implying that laboratory technicians are a thoroughly dishonest and inaccurate lot. I am implying that we, as physicians, are often guilty of accepting a report as being dependable when the young lady who has done the test may well be overworked or inexperienced. I am quite sure, in my own mind, that technical inexperience is a common

source of error in medical diagnosis and that the fault is as much ours in accepting questionable reports as theirs in occasionally presenting them to us.

A recent example may help me to explain this point. I was asked to review the blood smear of a five-year-old child. This child was an only son and had been ill for two weeks with fever and enlargement of the superficial lymph nodes and spleen. The technician doing the child's blood count had reported a total white count of 15,000 with 80 per cent of the cells classified as leukoblasts. On that report, the physician in charge had made a diagnosis of acute leukemia and had told the parents that the child would live not more than a very few weeks. The only difficulty with this particular problem lay in the fact that the cells recorded as leukoblasts happened to be normal, small lymphocytes. The correct hematologic diagnosis was lymphocytosis and not leukemia and fortunately for all concerned, the child has made an uneventful recovery.

Additional examples might be quoted almost indefinitely: the diagnosis of hyperthyroidism or hypothyroidism based on a basal metabolic determination made with a leaky apparatus; the diagnosis of diabetes mellitus as a result of a dirty test tube; or of nephritis for the same reason; or of septicemia due to contamination of the broth; or of hepatic insufficiency because all of the calculated dose of bromsulfalein was not injected into the vein. In each and all of these situations a serious and disturbing error in diagnosis may be made; in each a patient may be clinically mismanaged and even injured by our own basic mistake in accepting the report of the test without critical analysis and without intelligent judgment.

Conclusion.—As a general conclusion to this preliminary discussion, I should like to re-emphasize that it is our responsibility as physicians to see that the tests are accurately performed, to insist on dependable reports and to try to interpret these reports with clinical astuteness and experienced judgment. Please remember that the laboratory report should be an aid to diagnosis and not an alibi.

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LABORATORY ASSISTANCE IN THE DIAGNOSIS OF THE VENEREAL DISEASES

THE venereal group of diseases is usually considered to embrace the infections which are commonly transmitted by sexual contact. They are syphilis, gonorrhea, chancroid and lymphopathia venereum. A fifth entity, granuloma inguinale, is a cutaneous manifestation of leishmaniasis and is not encountered in the United States with sufficient frequency to render it an important factor in differential diagnosis.

SYPHILIS

The laboratory procedures pertaining to syphilis concern the identification of the causative organism by darkfield microscopy or by staining methods and the serum reactions which characterize the disease.

Darkfield Identification of Spirochaeta Pallida.—The causative organism of syphilis, Spirochaeta pallida, generally classed as a protozoon, is a delicate, closely spiraled, highly motile organism varying in length from 8 to 12 μ. Three motions are usually discernible in the fresh preparation, viz., rotation on long axis, bending and whipping, and forward and backward movement, during all of which the spiral contour is maintained. Because of low refractive index the body of the organism is not easily seen by direct illumination but becomes distinct by the darkfield method of illumination which utilizes a transverse beam of light. Under darkfield illumination the organism appears as a clear-cut, threadlike, colorless spiral against a dark background.

The darkfield examination is of assistance only in the early stages of syphilis, when the initial lesion or the cutaneous manifestations of the secondary stage are present. *Its efficacy is largely dependent upon the care with which the material to be examined is collected.* If the suspicious lesion is a genital ulcer, antiseptic dressing should not be applied prior to the collection of material for examination. The surface of the lesion should be gently abraded with gauze, the free blood removed and serum allowed to collect on the face of the ulcer. The serum may be transferred directly to the microscope slide or may be collected in a capillary tube for transport to the laboratory. As a rule, the examination should be carried out as soon after collection as possible. It is possible, however, to seal the capillary tube with wax and send the material through the mail to a central laboratory for the actual examination.

A single negative darkfield examination does not exclude the presence of the spirochete. At least *three* examinations should be made on different days. If all are negative the suspicion of the syphilitic nature of the lesion should not be lessened and the serology of the patient should be followed for a period of at least six months.

The importance of the darkfield diagnosis lies in the fact that a suspicious lesion may be properly classified at a time before the results of other laboratory methods become helpful. The institution of proper treatment at this early point in the course of the disease prevents the spread of infection to other persons and provides for the patient a more favorable prognosis as regards ultimate cure than at any subsequent period. Complete reliance cannot be placed upon the darkfield method of examination when the suspicious lesion involves the mouth, throat or anal region. In each of these sites there are frequently found saprophytic spiral forms which may readily lead to an erroneous diagnosis. The close resemblance of some of these forms to the Spirochaeta pallida may confuse even an experienced microscopist.

Staining Characteristics of Spirochaeta Pallida.—Probably the staining technic first utilized was the *India ink method* which is classed as a negative stain in that it colors all elements in the field with the exception of the organism. The method has a very limited practical use.

Since the discovery of the organism a large number of *aniline dyes* have been advocated as suitable for use in identifying Spir. pallida in suspected material. An efficient technic of this kind would have an enormous clinical value as it would permit the preparation of spreads and their transport to a central laboratory for the conduct of the actual examination. However, the consensus seems to be that no technic based upon aniline stains is sufficiently accurate or reliable to serve as a replacement for the darkfield.

The *silver impregnation methods* originated with Levaditi and have their principal utilization in the identification of the organism in tissue. Blocks of tissue are impregnated with a silver solution, the silver precipitated by a process closely resembling the development of a photographic plate, and the block sectioned. Subsequent modifications advocated the use of tissue sectioning before impregnation and development. Among the most widely used methods are the Warthin-Starry and Jahnel, and the Dieterle modification adapted for nerve tissue.

The conduct of any silver-staining technic requires rigid care in technic and in the preparation of the solution used. When stained by a silver method the organism appears dark brown or black against a lighter background. The extreme fineness and sharp contours which characterize the organism in the live state are largely lost. In tissue, also, the characteristic morphology becomes distorted and many atypical forms are encountered.

Serology of Syphilis.—All of the various serum and spinal fluid tests for syphilis are adaptations of two basic principles, viz., that of *complement fixation,* first described by Bordet-Gengou, and of *precipitation* or *flocculation,* originally studied by Michaelis. The original Wassermann test was the practical application of the complement-fixation principle. It has been modified in many cardinal respects, although the term still signifies any test procedure which utilizes the complement-fixation phenomenon. The Kolmer, Eagle and New York State modifications are probably the best known at the present time.

Of the flocculation group, the original workable method was sponsored by Meinicke. In the United States the Kahn, Kline, Hinton, Eagle and Mazzini methods are probably the most

widely used, although there are many others which represent adaptations of the precipitation principle.

Not any of these tests completely covers the field of syphilis. All have limitations and all may be influenced by certain disease entities other than syphilis. All are designed to measure the same reacting substance. The level of sensitivity of each test is arbitrarily set by the originator, although this level is subject to some latitude dependent upon the ingredients used, especially antigen. Also, the efficacy of performance is somewhat dependent upon the skill and care with which the test is carried out and upon the adherence to the technical details advocated by the originator. The use of short-cuts and personal modifications in technic almost invariably detracts from the basic efficiency of any method.

Interpretation of Serologic Results.—If carefully carried out by a trained technician and interpreted by a clinician of experience, any of the above methods is capable of guiding clinical syphilis work. Because of the inability to obtain complete agreement between any two or more tests, the use of multiple tests is considered to be desirable, especially in guiding the treatment of the disease. The information, however, must always be considered in the light of a carefully taken history and a reasonably complete medical survey.

With this latter information available, the inferences to be drawn from serologic tests may be bracketed into several fairly well defined groups:

I. *Serum Negative to All Tests.*—The first and largest group is composed of individuals whose serum is negative to all tests. The question arises as to the justification for considering that the component members are free from a reasonable suspicion of infection.

It must be admitted that the following types of infection might escape detection:

1. Syphilitic infection in the early stage (primary) before the serologic response has developed.
2. Debilitated or "burnt out" tabes or congenital syphilis.
3. Infections which have been treated to a point where the serum is negative to all tests.
4. Certain types of central nervous system disease in which the spinal fluid only is positive.

5. Patients who display atypical reactions known as *zone phenomena* in which a strongly positive serum may fail to show a positive reaction until diluted.

With these exceptions, the majority of which are detectable through medical survey and careful history, the mathematical possibility of any appreciable number of patients with syphilis escaping detection is remote.

II. *Serum Positive to All Tests.*—The second important group of patients are those whose serum reacts positively to all tests. The initial step with this group is the repetition of the test in order to guard against a possible laboratory error. If the repeat findings are similar and the patient displays clinical evidence or gives a history of infection or treatment, the case may be readily classified. Without clinical findings and history, the patient should be carefully studied, especially for evidence of central nervous system or cardiovascular involvement. In event of negative findings and after excluding the possible influence of intercurrent illness, the abstract diagnosis of syphilis should be a matter for measured decision by the clinician. The laboratory can be of no further assistance.

If *supersensitive* test methods, such as the Kahn presumptive and Kline exclusion, are employed, their findings should be interpreted only in the light of clinical knowledge. These methods are not considered to be free from nonspecificity.

III. *Serum Weakly Positive to Some Tests and Negative to Others.*—The troublesome group of patients are those whose serum is weakly positive to some tests and doubtful or negative to others. This is a picture frequently encountered in treated syphilis and sometimes in the group of exceptions mentioned above. It is not the expected picture of untreated and established syphilis. The interpretation of this type of findings should be attempted with great caution, when not supported by history of clinical evidence.

Thus, within reasonable limitations, the results of well performed serologic tests for syphilis form a reliable indicator to the possible presence of the disease. It is impossible to make allowances for the vagaries which may result from poor laboratory work. The tests are of greatest value when their interpretation is coordinated with the clinical findings and a truthful history. In the small percentage of individuals in which there

are low-reading positive or doubtful findings, without the support of clinical evidence or history, the final decision must be based upon sound clinical judgment. On the whole, the reliability of well conducted serologic tests compares favorably with many other laboratory aids upon which the medical man depends for the confirmation of a clinical impression.

Spinal Fluid Examination.—The cell count, total protein determination, albumin-globulin ratio, the colloidal reactions, and complement-fixation and precipitation tests are usually carried out in spinal fluid. In each of these determinations the reliance to be placed upon the findings must be predicated upon the freedom from contamination of the fluid by whole blood introduced during the spinal puncture. Any appreciable amount of blood will distort the findings.

The *cell count* should be carried out as soon after the collection of the specimen as possible. A count of ten lymphocytes or less is considered to be within the range of normal. The higher counts are usually interpreted to indicate the presence of irritative phenomena within the central nervous system.

Noguchi and Pandy methods are the most frequently used in the determination of the *total protein.* The reagents for these procedures are designed to give positive findings when the total protein is above the normal limits. Other procedures are available for the more accurate quantitative determination of total protein and globulin and from these findings the *albumin-globulin ratio* may be determined. All of the procedures are based upon the precipitation of the various protein fractions.

Of the *colloidal tests* the best known are the colloidal gold, gum mastic and benzoin. The findings of all of this group are nonspecific in nature, in that they are not dependent upon the presence of syphilis nor do they contribute reliable data as to the type of disease when syphilis is present.

Complement-fixation and *precipitation tests* follow the same general technic as recommended for serum studies. Because of the importance attached to a positive reaction in spinal fluid and the difficulty in obtaining a repeat specimen in case of inconclusive results, the utmost technical care should be observed in conducting the various tests. A positive result in a carefully controlled complement-fixation test, except in exceed-

ingly rare instances, is specific for syphilis. Negative findings are of almost equal importance when considered with the treatment, history and physical findings.

GONORRHEA

The identification of the gonococcus (Neisseria gonorrhoeae) is confined to two general procedures, viz., the recognition of the organism in stained spreads and its growth on artificial media.

Staining of the Gonococcus.—Although the organism may be stained by many of the aniline dyes, the *Gram technic* alone should be used in routine work. The recognition of other than typically arranged intracellular forms becomes difficult without the assistance of the gram-negative characteristic.

In acute disease of both men and women the *spread method* may serve as an efficient confirmation of diagnosis due to the relative frequency with which the classical arrangement of the organism within a leukocyte is encountered. In disease of long standing, especially in women, and as a criterion of cure in both men and women, the Gram-stained spread loses much of its value. In preparations which do not present an entirely typical picture, the conclusion as to the presence or absence of the organism becomes, to a large extent, a personal opinion of the microscopist.

The Gram technic should be carried out with extreme care. Equally important is the scrutiny to which the preparations are submitted. An inexperienced or careless microscopist should not be entrusted with this task, nor should the pressure of work militate against the detailed and searching inspection of each preparation.

Culture Identification of the Gonococcus.—The use of the culture method of establishing the presence of the gonococcus has assumed greater importance in recent years, as a result of various studies which indicate its marked superiority over the spread technic. This superiority is most pronounced in atypical disease in men, in infection of considerable standing in women, and as a criterion of cure in both instances. It must be stated, however, that the greater efficiency of the culture technic is only relative, as there appear to be many infections,

especially in women, in which the culture findings do not support the clinical picture. In known prostitutes with clinical evidence of disease a substantiated diagnosis is possible in only 25 per cent by repeated and careful culture studies.

Media.—A large number of media have been recommended for the growth of the gonococcus. Probably the most generally satisfactory media are the Douglas *chocolate agar* and the *horse serum medium* of Pizer. Incubation at 35° C. for forty-eight hours in an atmosphere of increased carbon dioxide content is the usual practice. The colonies are small, clear-cut, translucent and will give a positive oxidase reaction. Further confirmation is obtained by fermentation reactions with various sugar media, the gonococcus being the only member of the Neisseria group which will ferment glucose. Whenever possible, all cultures upon which a positive diagnosis is to be based should be carried through the sugar reactions in order to guard against errors due to the occasional presence of nonpathogenic Neisseria which closely simulate the gonococcus.

A suitable medium has not been developed which will permit the transportation of the specimen through the mail to a central laboratory, as is practiced in diphtheria. At this time it is essential that the suspected material be plated and placed in the incubator within a reasonable time (four hours) after collection. The most satisfactory results are obtained when the time interval between collection and plating is reduced to the minimum.

Collection of Material.—The collection of the material to be cultured is highly important to the success of the culture study, especially in women. Secretions from the cervix should be secured after the area has been cleansed by sponging away the accumulated discharge and removing the mucous plug. The use of the leaves of the bivalve speculum as a means of expressing secretion from the cervical canal is helpful. Urethral secretions should be obtained, following gentle pressure upon the canal by the examining finger. Skene's glands should also be emptied and the material collected. In most instances the collection is carried out with cotton-tipped applicators which are placed in a tube containing a small amount of broth. This carrying tube is then sent to the laboratory for plating.

The Diagnosis of Vulvovaginitis.—The laboratory methods used for the diagnosis of specific vulvovaginitis in infants or children are essentially the same as those used for other types of suspected gonococcal infection. *In collecting material* for spread or culture, the secretion of the vagina is used, rather than that of the cervix or urethra. This is based upon the fact that the vaginal mucous membrane is susceptible to infection in childhood but extremely resistant during adult life. The vaginal secretion is secured by alternate injection and aspiration of 2 cc. of broth, using a rubber catheter and syringe. It is generally considered that the spread method of diagnosis should not be relied upon to the same degree as in adult infection, due to the presence, among the normal bacterial flora, of gram-negative diplococci which may be confused with the gonococcus.

CHANCROID

The soft chancre is an acute destructive ulcer which usually occurs in the genital region. Although there are no reliable statistics available as to the prevalence of the condition, it is generally believed that a definite decline in incidence is under way. From a clinical, as well as from the laboratory viewpoint, the important feature of chancroid lies in the frequency with which the lesion may also harbor the organism of syphilis. All chancroids should be considered as chancres and be subjected to repeated darkfield examinations for Spirochaeta pallida. Blood tests for syphilis, both complement-fixation and flocculation, should be done at frequent intervals during the course of the disease and for a period of at least six months after the healing of the lesion.

The *causative organism* of chancroid is an extremely small bacillus which is stained with some difficulty with the ordinary dyes and is negative to the Gram method. It can be cultivated from material taken from the base of the chancroid or from pus aspirated from a chancroidal bubo. The organism is not pathogenic for laboratory animals.

In addition to the cultivation of the organism for diagnostic purposes, pure cultures have been used for the production of an antigen for use in skin testing in suspected cases. The *Ito-Reenstierna intradermal test* for chancroidal infection may be used as an aid for the clinical diagnosis. The test is performed

by injecting a small amount of the antigen intradermally and reading in forty-eight hours as in the Frei test. The antigen is prepared from culture medium containing the infectious organism. A positive reaction to the test indicates that the subject has at some time suffered a chancroidal infection.

LYMPHOPATHIA VENEREUM (LYMPHOGRANULOMA INGUINALE)

Lymphopathia venereum, which is caused by a filtrable virus, is characterized by acute adenitis of the regional lymph glands that often suppurate and produce sinus tracts; and later by the manifestations of the disabling anorectal complications.

The clinical diagnosis of the lesion may be confirmed by examinations of the tissues removed from the infected areas or by the intradermal Frei test.

The Frei Test.—The original *Frei antigen* was prepared by subjecting the diluted purulent matter obtained from a suppurative bubo to fractional sterilization. Later, modifications in the preparation of antigen were employed to remove the excess protein and hemorrhagic elements, thereby producing a more satisfactory and esthetic preparation for clinical use. Frei antigens prepared from material taken from known cases of the disease are not always potent. Not infrequently they fail to produce a positive reaction in known cases of the disease and must be discarded. Antigens may frequently lose their potency after six months.

The successful therapeutic effect of the sulfonamide compounds in the past three years has caused a marked diminution in the number of human sources of antigenic material. Mouse-brain antigens have been employed, but appear to produce a certain number of nonspecific reactions. Other animal and artificial cultural preparations have not yielded an antigen which serves as a reliable diagnostic aid in lymphopathia venereum.

The Frei test is performed by injecting 0.1 cc. of Frei antigen intradermally on the volar aspect of the forearm and reading the reaction at forty-eight and seventy-two hours. The presence of a definite indurated intradermal nodule surrounded by a bordering ring of acute redness is considered a positive reaction. A positive reaction indicates that the subject has had the disease which may or may not be clinically active at the time of testing.

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DIFFERENTIAL DIAGNOSIS OF JAUNDICE

By Combined Serum Phosphatase Determination and Cephalin Flocculation Test

A NUMBER of laboratory methods are employed to aid in establishing the presence and degree of disease of the liver and biliary tract. Representative of those in more common use are the following, classified according to the physiologic mechanisms involved:

I. *Measures of disturbed metabolism or excretion of bile pigments:*
   1. Determination of serum bilirubin or icteric index.
   2. Van den Bergh reaction.
   3. Qualitative tests for bile pigments in the urine and stools.

II. *Measures of the capacity of the liver to perform certain functions ("liver function" tests):*
   1. To excrete into the bile endogenous bile pigments (the bilirubin tolerance test[1]) or exogenous dyestuffs (the bromsulfalein retention test[2]).
   2. To utilize certain carbohydrates (the galactose tolerance test[3, 4, 5]).
   3. To detoxify or metabolize selected compounds by conjugation with substances formed by the liver (the hippuric acid excretion test[6, 7]).
   4. To elaborate various substances such as prothrombin,[8, 9] serum albumin and cholesterol esters.[9, 10]

III. *Measures of the formation of certain abnormal substances by the disordered liver:*
   1. Determination of serum globulins.
   2. Takata-Ara test.
   3. Cephalin flocculation reaction.[11]

IV. *Measures of the patency of the biliary tract:*
   1. Quantitative estimation of stool and urinary excretion of urobilinogen.[12, 13]
   2. Duodenal drainage.

3. Cholecystograms and cholangiograms.
4. Determination of free cholesterol in the serum.[9]
5. Serum phosphatase determination.[14]
6. Several of the tests mentioned under I and II.

The tests of the first group indicate the degree and the trend of the patient's icterus, distinguish between hemolytic and nonhemolytic jaundice, and may be of aid in differentiating obstructive from hepatogenous jaundice. The intensity of jaundice, however, is an uncertain guide to the extent of liver and biliary tract involvement. Little or no jaundice may accompany advanced cirrhosis, extensive liver metastases, acute or chronic cholecystitis, or stone in the common bile duct.

The aim of the tests comprising the second group is to detect liver damage by demonstrating diminished performance of one or another of the many liver functions. The chief difficulty here is that extensive *morphologic* changes (which may be important clinically) may involve the liver without causing demonstrable *functional* impairment. The bromsulfalein retention test is a relatively sensitive indicator of liver damage. Cirrhosis, fatty degeneration, chronic passive congestion, diffuse carcinomatosis of the liver—all cause significant retention of bromsulfalein prior to the appearance of jaundice; and the degree of retention is a rough measure of the extent of liver involvement.[2] The test does not differentiate these conditions, however, nor does it add significantly to the study of the definitely jaundiced patient. The determination of cholesterol esters, the hippuric acid excretion test and the galactose tolerance test serve a twofold purpose: they help to differentiate hepatogenous from obstructive jaundice and, if icterus is of the hepatogenous type, they indicate the severity of liver parenchymal damage. The determination of prothrombin has become indispensable in estimating bleeding tendencies and in the regulation of treatment therefor.

The third group comprises tests that depend, not upon any decreased liver function, but upon the formation of certain abnormal substances, probably globulins. These substances appear in the blood stream in cirrhosis and in hepatitis.

The fourth is a heterogeneous group of methods for investigating the biliary tract. The use of cholecystograms and cholangiograms, and the study of bile obtained by duodenal

drainage, are well established procedures. A precise but laborious means for estimating the patency of the biliary tract is afforded by the quantitation of fecal and urinary excretion of urobilinogen[12, 18]; in this way cancerous occlusion of the common or main hepatic ducts can be differentiated from other causes of jaundice. The level of free cholesterol and of phosphatase activity in the serum depend, in part, upon the patency of the biliary tract and increase with biliary obstruction.

Laboratory Procedures Employed in the Differential Diagnosis of Nonhemolytic Jaundice.—*General Considerations.*—Many of the laboratory methods used in the study of various aspects of liver disease are inapplicable to the special problem of the differential diagnosis of jaundice. For example, both obstructive and hepatogenous jaundice cause marked retention of bromsulfalein. Some tests, however, are much more affected by liver parenchymal damage than by biliary obstruction. Others are much more sensitive to obstructive processes in the biliary tract than to hepatic cell injury. Such tests may be employed to differentiate hepatogenous from obstructive jaundice, as indicated by the following classification of methods commonly used:

I. *Tests for hepatogenous jaundice:*
1. Determination of serum cholesterol esters.
2. Hippuric acid excretion test.
3. Galactose tolerance test.
4. Cephalin flocculation reaction.

II. *Tests for obstructive jaundice:*
1. Determination of free or total serum cholesterol.
2. Determination of serum phosphatase activity.

The tests comprising the *first group* afford evidence of inflammatory or degenerative changes in the liver parenchyma and are helpful in the recognition of hepatitis and other forms of "medical" jaundice. The group as a whole has certain limitations, however. If the tests are employed in patients with jaundice due to biliary tract obstruction, negative results are usually obtained. The diagnosis of obstructive jaundice (with its indications for surgical intervention) must be made, therefore, by exclusion; *i.e.*, on the basis of absence of demonstrable liver parenchymal damage in jaundiced patients.

Moreover, if obstruction is protracted, the findings may be equivocal or misleading due to the supervention of infection or secondary parenchymal damage.

The tests comprising the *second group* serve chiefly to demonstrate obstructive processes in some part of the biliary tree. In cases with incomplete or intermittent biliary obstruction, however, the results may be indecisive or in error. Negative findings are the rule in hepatogenous jaundice, which is diagnosed by exclusion.

These limitations account for the general experience that no one method has proved wholly adequate for the differential diagnosis of jaundice. Increased accuracy in diagnosis is not attained, however, by indiscriminate multiplication of tests. The limitations indicated being common to all the tests in each group, they cannot be obviated by the repetitious use of several methods in the same group.

By selecting methods so as to combine a test for hepatogenous jaundice with one for obstructive jaundice, it is possible to compensate in part for the limitations inherent in each type of test. As is quite evident, the two categories of tests are *complementary:* one group provides positive evidence for the diagnosis of that type of case for which the other provides merely negative evidence. Using such a combination of complementary methods, if a case of icterus gives a positive result for biliary occlusion and a negative result for hepatitis, reciprocal confirmation of the diagnosis of obstructive jaundice is afforded. If the findings are negative for obstruction and positive for hepatitis, the diagnosis of hepatogenous jaundice is doubly checked. If the tests give results with conflicting diagnostic implications, then both obstructive and parenchymal factors are operative; or the one or the other test is in error. In either event, cautious interpretation is indicated and further clinical observation and additional laboratory studies are necessary.

This plan for the differential diagnosis of jaundice has been in operation at the Presbyterian Hospital for almost three years. We have employed the determination of serum phosphatase activity as an index to biliary tract obstruction[14, 15] and the cephalin flocculation reaction as a test for liver parenchymal damage.[11] The results obtained with each of these procedures

alone are first considered, then the significantly improved diagnostic results of their combined use are presented.

SERUM PHOSPHATASE DETERMINATION IN THE DIFFERENTIAL DIAGNOSIS OF JAUNDICE

Blood serum contains one or more phosphatases, enzymes capable of splitting off inorganic phosphate from certain organic phosphoric esters. The amount present in serum can be measured accurately in terms of enzymic activity; in normal adults there are 1 to 4 Bodansky units per 100 cc., as determined by the Bodansky method[16] employed by us. Most of the serum phosphatase is derived from the bones, whence it escapes into the blood to pass through the liver and be excreted in the bile.

The phosphatase activity of the serum is increased chiefly in two types of disease: in certain disorders of the bones in which more enzyme is formed; and in certain disorders of the liver and biliary tract in which the excretion of bile is interfered with and the enzyme tends to accumulate in the blood. This latter circumstance can be utilized to differentiate between obstructive and hepatogenous jaundice[14] because, in general, occlusion of the extra- or intrahepatic biliary tract causes larger amounts of phosphatase to appear in the blood than are associated with inflammatory or degenerative changes in the liver parenchyma.

Serum phosphatase values in most cases of jaundice due to common duct obstruction exceed 10 Bodansky units per 100 cc. serum, whereas in most cases of "catarrhal" jaundice levels less than 10 Bodansky units are found. This is illustrated by our experience with the determination as summarized in Table 1. Values greater than 10 Bodansky units were obtained in approximately 91 per cent of sixty-nine proved cases of noncalculous (chiefly carcinomatous) obstruction of the common duct; and in approximately 76 per cent of fifty-eight proved cases of stone in the common duct. These two groups together comprise a total of 127 proved cases of common duct obstruction, of which 107 or 84 per cent yielded phosphatase levels of over 10 Bodansky units per 100 cc. serum. Of 108 cases classified clinically as "catarrhal" jaun-

dice, only fifteen or about 14 per cent were found to have serum phosphatase values over 10 Bodansky units.

Our data in these and other forms of liver and biliary tract disease[14] indicate that in icteric patients with serum phosphatase levels less than 10 Bodansky units, it may be inferred that jaundice is probably not of the obstructive type. We find the determination of definite value in the differential diagnosis of jaundice but certain *limitations* should be emphasized: (1) The test failed to indicate common duct obstruction in almost 25 per cent of our proved cases of choledocholithiasis (a con-

TABLE 1

RESULTS OF SERUM PHOSPHATASE DETERMINATIONS IN 127 ADULTS WITH JAUNDICE DUE TO OBSTRUCTION OF COMMON BILE DUCT* AND IN 108 ADULT CASES OF "CATARRHAL" JAUNDICE

Type of Jaundice	No. of Cases	Serum Phosphatase Values (Bodansky Units per 100 cc. Serum)					
		4.1 to 9.0	9.1 to 12.0	12.1 to 25.0	More than 25	More than 10.0	Less than 10
1. *Noncalculous obstruction* due to							
Carcinoma head of pancreas	29	2	1	15	11	26	3
Carcinoma common duct	20	2	2	10	6	18	2
Carcinoma gall bladder	6	0	0	4	2	6	0
Miscellaneous causes	14	1	1	8	4	13	1
Total, noncalculous obstruction	69	5	4	37	23	63	6
2. *Calculous obstruction*	58	11	8	35	4	44	14
Total, calculous and noncalculous obstruction of common duct	127	16	12	72	27	107	20
3. *"Catarrhal" jaundice*	108	84	15	8	1	15	93

* Only cases of obstructive jaundice proved at operation or autopsy are included in this table.

dition in which obstruction is likely to be incomplete or intermittent). (2) There is some overlapping of values in the obstructive and hepatogenous groups, about 15 per cent in either direction in our experience to date. Some investigators find a much higher percentage of overlapping.[17, 18] (3) Application to the differential diagnosis of jaundice demands careful and consistent technic in the determination of serum phosphatase, since relatively small differences may be significant in some cases. (4) The determination is not applicable in the presence of certain bone diseases and the findings are difficult of interpretation in jaundiced children.[14]

THE CEPHALIN FLOCCULATION REACTION IN THE DIFFERENTIAL DIAGNOSIS OF JAUNDICE

The cephalin flocculation test consists of adding a colloidal suspension of cephalin and cholesterol to the patient's serum diluted 1:21 with normal saline, then after twenty-four to forty-eight hours, noting the degree of flocculation and precipitation of lipids in the test tube.[11] The sera of normal individuals or of patients with diseases not accompanied by active liver disturbances cause no flocculation. Typical cases of hepatitis ("catarrhal" jaundice) or of active cirrhosis, on the other hand, usually give a strong (4+ or 3+) reaction, which becomes negative as the hepatic disorder subsides.

TABLE 2

RESULTS OF CEPHALIN FLOCCULATION REACTION IN JAUNDICE DUE TO OBSTRUCTION OF COMMON BILE DUCT AND IN "CATARRHAL" JAUNDICE

	No. of Cases	Cephalin Flocculation Test				
		++++	+++	++	+	Negative or ±
1. Obstructive jaundice.	77	0	0	1	6	70
2. "Catarrhal" jaundice.	60	37	11	6	2	4

Positive reactions are due, apparently, to subtle changes in the globulin fraction of the serum occurring with certain types of inflammatory and degenerative liver derangements. The cephalin flocculation test therefore reflects irritation of hepatic cells by disease. It is not dependent upon impairment of a liver function, which may become apparent only after extensive liver damage.

Negative results are usually obtained in obstructive jaundice, if the test is properly performed, and this forms the basis for its application to the differential diagnosis of jaundice (Table 2). Of seventy-seven proved cases of common duct obstruction studied at the Presbyterian Hospital, seventy gave negative results, none were strongly positive; whereas of sixty cases of "catarrhal" jaundice, forty-eight gave strongly positive results, only four were negative. We have found the

cephalin flocculation reaction of definite value in differentiating these two common causes of jaundice.

Certain *sources of error* should be noted. Cholangitis accompanying obstruction of the bile ducts may cause sufficient disturbance of the liver parenchyma to give a weakly positive test. Some cases of rapidly subsiding hepatitis, though the patient is still deeply jaundiced, may give negative results. In certain diseases, such as virus pneumonias, infectious mononucleosis, subacute bacterial endocarditis and disseminated lupus erythematosus, positive cephalin flocculation reactions are obtained frequently; these positive results possibly reflect liver damage that may not be obvious clinically or even histologically.

With regard to technical sources of error, it should be appreciated that cephalins differ in sensitivity. The most satisfactory are the cruder preparations which have been "ripened," *i.e.*, darkened by exposure to air and sunlight.[11] Fresh, highly purified cephalins form extremely sensitive emulsions suitable for detecting very slight liver parenchymal damage but are not applicable to differentiating "catarrhal" from obstructive jaundice. Gross bacterial contamination may cause false positive reactions and excessively warm or cold rooms may affect the results.

RESULTS OBTAINED BY COMBINING THE SERUM PHOSPHATASE DETERMINATION WITH THE CEPHALIN FLOCCULATION TEST

An analysis of our cases of obstructive, "catarrhal" and hemolytic jaundice studied by both methods is given in Table 3. The last three columns indicate the incidence of diagnostic errors incurred by the serum phosphatase determination alone, the incidence of errors incurred by the cephalin flocculation reaction alone, and the number of times that both methods gave misleading results in the same case. Thus far, both tests have not been found to be in error in any one case either of "catarrhal" jaundice or of jaundice due to demonstrated common duct obstruction. Our experience indicates that, in general, (1) the diagnosis of common duct obstruction is highly improbable if the serum phosphatase level is *below* 10 Bodansky units and the cephalin flocculation test is strongly *positive;* (2) the decision to explore icteric patients, based on clinical

grounds, is supported by finding a serum phosphatase level *over* 10 Bodansky units associated with a *negative* cephalin flocculation reaction. In evaluating our data, however, the fact should not be overlooked that a significant proportion of cases (Table 3) gave results with conflicting diagnostic implications, difficult of interpretation. And some particularly complex cases are not represented in Table 3 because the cause of jaundice was not made clear even at operation or autopsy.

TABLE 3

ANALYSIS OF CASES OF OBSTRUCTIVE JAUNDICE, "CATARRHAL" JAUNDICE AND HEMOLYTIC JAUNDICE STUDIED BY BOTH METHODS (SERUM PHOSPHATASE DETERMINATION AND CEPHALIN FLOCCULATION TEST)

Type of Jaundice	Serum Phosphatase		Cephalin Flocculation			In Disagreement with Final Diagnosis		
	Below 10 Bod. Units	Above 10 Bod. Units	Neg.	Weakly Pos.	Strongly Pos.	Serum P'tase Alone	Ceph. Flocc. Alone	Both Methods
1. *Common duct obstruction;*								
A. Calculous (34 proved cases).	7	27	30	4	0	7	3	0
B. Noncalculous (39 proved cases).....	5	34	33	6	0	5	3	0
Total obstructive jaundice (73 proved cases).	12	61	63	10	0	12	6*	0
2. *"Catarrhal" jaundice* (66 cases)..	57	9	12	5	49	9	12*	0
3. *Hemolytic jaundice* (14 cases).....	14	0	11	1	2	0	3	0

* A ++, +++, or ++++ cephalin flocculation reaction is considered to be in disagreement with the diagnosis of obstructive jaundice; a negative, ± or + reaction is considered to be in disagreement with the diagnosis of "catarrhal" jaundice.

In *hemolytic jaundice* (Table 3), serum phosphatase values are consistently within normal limits and the cephalin flocculation reaction is usually negative. These results are of largely academic interest, however, since more specific methods for the diagnosis of hemolytic jaundice are available.

The cephalin flocculation test proved useful in differentiating hepatomegaly due to *nonbiliary cirrhosis* from hepatomegaly due to *fatty degeneration, chronic passive congestion* or *metastatic involvement.* Strongly positive reactions, usually associated with definite hyperglobulinemia, were obtained in the majority of cases showing active hepatic cirrhosis at op-

eration or autopsy* (Table 4); whereas most patients with fatty, congested or carcinomatous livers gave negative cephalin flocculation reactions. The serum phosphatase determination sometimes proved useful as a relatively early indicator of metastatic involvement of the liver in patients known to have carcinoma, and in some cases of liver abscess. The results in both groups, however, were erratic (Table 4). In most cases of cirrhosis, the serum phosphatase levels were less than 12 Bodansky units per 100 cc. serum, except when associated with marked jaundice or primary liver carcinoma. All our

TABLE 4

ANALYSIS OF RESULTS IN MISCELLANEOUS DISORDERS OF THE LIVER AND BILIARY TRACT

Type of Jaundice	Serum Phosphatase		Cephalin Flocculation			
	Below 10 Bod. Units	Above 10 Bod. Units	++++ or +++	++	+	Neg. or ±
1. *Postarsphenamine jaundice*						
A. Clinically of hepatogenous type (26 cases)	21	5	16	2	2	6
B. Clinically of obstructive type* (11 cases)	1	10	2	0	0	9
2. *Hepatic cirrhosis* (nonbiliary) (37 proved cases)	28	9	22	4	1	10
3. *Metastatic carcinoma of liver* (15 proved cases)	6	9	1	3	0	11
4. *Primary carcinoma of liver*						
A. Cholangioma (4 proved cases)	1	3	0	0	0	4
B. Hepatoma (5 proved cases)	2	3	2	0	0	3
5. *Liver abscess* (15 cases)	7	8	6	1	0	8
6. *Chronic passive congestion of liver*† (9 proved cases)	9	0	2	1	0	6

* The incidence of cases of the obstructive type in our series is very high because of the addition of referred patients.

† The positive cephalin flocculation results were all obtained in cases of subacute bacterial endocarditis with cardiac failure.

proved cases of chronic passive congestion of the liver yielded serum phosphatase values less than 10 Bodansky units (Table 4).

The results in *postarsphenamine jaundice* are of particular interest (Table 4). The findings in the majority of patients were indicative of hepatogenous jaundice, as anticipated. However, marked elevations in serum phosphatase activity

* Negative results were obtained in some cases of cirrhosis, particularly in patients with normal serum globulin levels. The clinical course in this group suggests that liver parenchymal damage was mild and only slowly progressive.

together with negative cephalin flocculation reactions were obtained in some instances, suggesting that icterus was due to biliary tract obstruction. In this "obstructive" group, characteristic symptoms, including jaundice, invariably developed after the second or third injection of arsenicals. The clinical course so strongly suggested common duct obstruction that four patients were explored. The common bile duct was found to be patent in every instance. Liver biopsies confirmed the absence of significant parenchymal damage and disclosed evidence of injury to the finer biliary radicles, with intrahepatic obstruction. The cases in question appear to represent a distinct type of arsphenamine hypersensitivity[19] particularly affecting the smaller branches of the biliary tree. Studies now in progress indicate that a similar obstructive mechanism may operate in the production of jaundice by other drugs. In these and in related problems of liver disease, we have found that the combined use of the serum phosphatase determination and the cephalin flocculation reaction is particularly helpful in dissociating obstructive from parenchymal factors.

SUMMARY

The available laboratory aids for the differential diagnosis of jaundice are classified into two groups: tests for hepatogenous jaundice and tests for obstructive jaundice. The tests comprising each group have certain limitations in common which are not obviated by reduplication of methods within the group. Combining a test for hepatogenous jaundice with one for obstructive jaundice partially compensates for these limitations, at the same time providing reciprocal confirmation of the results. We have found that accuracy of differential diagnosis in jaundice is increased by such combined use of complementary methods. Illustrative data are presented, in which the serum phosphatase determination served as an index to biliary tract obstruction and the cephalin flocculation reaction as a test for liver parenchymal damage.

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HISTAMINASE: EXPERIMENTAL AND CLINICAL STUDIES

THERE has been renewed interest in the research and clinical aspects of the substance, histaminase, discovered by Best and McHenry[1] in 1930. Roth and Horton[2] and Baker[3] have reported its usefulness in *physical allergy* to cold; Foshay and Hagebusch[4] have discussed its value in *serum sickness;* Layman and Cumming[5] and Forman[6] have reported its use as a valuable adjunct to other therapeutic measures in *urticaria* and *angioneurotic edema.* In January of this year, Eustis[7] reported four cases of *asthma* which were treated by histaminase with good results. Adelsberger[8] and Ertl[9, 10] have suggested its use in *allergic rhinitis,* Ertl[9, 10] advocating it as a nasal spray in this disease and in *hay fever.* In his reports the latter was benefited, the former was not. Blecha[11] has used the drug with beneficial results in cases of *infantile eczema.* Such reports have stimulated new inquires into the properties of histaminase and, chiefly, into the manner in which it acts in allergic conditions.

It has long been held by some investigators, notably, Dragstedt, Gebauer-Fuelnegg,[12, 13] Bartosch, Feldberg and Nagel[14] that the combination of antigen and specific antibody in the allergic individual results in the release of histamine or a histamine-like substance, which is directly responsible for most of the allergic manifestations. Karady[15] and others have tried to show this possible relationship experimentally. Accordingly, it recently has been hoped by many investigators[16, 17] that histaminase, a substance apparently enzymic in nature[1] which specifically inactivates histamine *in vitro,* might

be capable of inactivating it *in vivo*, and thus be instrumental in preventing or relieving allergic phenomena caused by the theoretical presence of histamine in the shock organs.

Our attention has been focused upon two relatively recent reports, by Farmer[18, 19] and Karady.[20] Farmer, elaborating the relation between histamine and anaphylaxis, claimed that if he sensitized guinea pigs to horse serum and, at the height of sensitivity two weeks later, started injections of histamine for twelve to eighteen days, the isolated uterine horns would become relatively refractory to histamine administered in a water bath according to the Dale technic. Karady[20] stated that normal guinea pigs, injected with histaminase intravenously, were protected against 4 mg. of histamine injected intraperitoneally fifteen minutes later, while the controls died; also that egg white sensitized guinea pigs, injected with histaminase intravenously, were protected from anaphylactic shock fifteen minutes later, when an anaphylactic dose of egg white was injected intra-abdominally. We investigated the essential findings of these important reports in the following experiments.

EXPERIMENTAL STUDIES

Controls.—Thirty male guinea pigs, average weight 200 to 300 gm., were sensitized to normal horse serum by subcutaneous injections in the abdominal regions of 1 cc. of a 1:10 dilution of horse serum. Fifteen days later 1 cc. of horse serum, in varying dilutions, was injected intrajugularly without narcosis.

Table 1 indicates that 1:10 and 1:7.5 dilution approximates the minimal lethal dose. A dilution of 1:2 was definitely lethal. Although typical anaphylactic convulsions occurred in animals at a 1:15 dilution, two animals recovered from convulsions and survived. In the animals that died, convulsions usually began within three minutes and never after nine.

Histamine.—Twenty-two male guinea pigs of average weight, namely, 200 to 300 gm. were divided into two groups. In the first group of nine, each animal was given daily injections subcutaneously of histamine in the form of the phosphate salt. After seven days all the animals were sensitized with 1 cc. of a 1:10 dilution of horse serum subcutaneously, and

the histamine injections were discontinued. In the second group of thirteen, daily injections of histamine were continued for fourteen days after the sensitization with horse serum. The histamine dosage varied in the different animals from 0.002 mg. to 0.5 mg. daily. Fifteen days after the sensitizing

TABLE 1

CONTROL GROUP, HORSE SERUM SENSITIZATION, DILUTION OF ANAPHYLACTIC DOSE AND RESULTANT MAJOR SYMPTOMS

Number of Animals	Dilution of Horse Serum	Dyspnea			Convulsions		Death
		Slight	Moderate	Severe	Slight	Severe	
2	1 : 100	..	..	..	..	..	0
1	1 : 25	..	.	..	..	..	0
3	1 : 15	..	.	3	..	3	1
5	1 : 10	..	..	4	..	3	3
6	1 : 7.5	..	1	5	1	4	4
12	1 : 2	..	..	12	..	12	12
1	1 : 1	..	..	1	..	1	1

dose of horse serum, each animal received 1 cc. of horse serum intrajugularly. The dilutions that were used varied from 1:2 to 1:10.

TABLE 2

SEVEN-DAY HISTAMINE GROUP. HORSE SERUM SENSITIZATION, DILUTION OF ANAPHYLACTIC DOSE AND RESULTANT MAJOR SYMPTOMS

Histamine Dosage, mg.	Number of Animals	Dilution of Horse Serum	Dyspnea			Convulsions		Death
			Slight	Moderate	Severe	Slight	Severe	
0.002	1	1 : 10	1	.	.	.	.	0
0.02	3	1 : 7.5	.	1	2	2	1	0
0.02	1	1 : 2	.	1	.	1	.	0
0.1	1	1 : 10	.	.	1	.	1	1
0.2	2	1 : 2	1	2	.	2	.	0
0.5	1	1 : 10	.	.	1	.	1	1

Table 2 shows that practically every animal suffered moderate or severe dyspnea and slight or severe convulsions—symptoms of shock. In some cases these were delayed in their onset for nine or ten minutes. However, of the nine animals receiving an anaphylactic dose of horse serum in a dilution of

1:10 or stronger, only two, or 14 per cent, died, in comparison with seventeen deaths, or 74 per cent fatality in the twenty-three controls receiving such dilutions.

Table 3 discloses that when the histamine injections were prolonged to twenty-one days, the results were generally better. Less symptoms of a severe nature were encountered. The deaths numbered two or 15 per cent, again considerably less than the controls.

With a somewhat steplike regularity, the animals which received the greater doses of histamine were tolerant to greater doses of horse serum. On a weight basis, 0.002 mg. corresponds with a 0.5-mg. dose for a 62-kg. human—an amount

TABLE 3

TWENTY-ONE-DAY HISTAMINE GROUP. HORSE SERUM SENSITIZATION, DILUTION OF ANAPHYLACTIC DOSE AND RESULTANT MAJOR SYMPTOMS

Histamine Dosage, mg.	Number of Animals	Dilution of Horse Serum	Dyspnea			Convulsions		Death
			Slight	Moderate	Severe	Slight	Severe	
0.002	2	1 : 1	.	1	1	.	1	1
0.01	1	1 : 10	.	.	.	.	.	0
0.02	1	1 : 5	.	1	.	1	.	0
0.02	2	1 : 2	.	1	1	.	.	0
0.02	1	1 : 1	.	.	1	.	1	1
0.1	1	1 : 5	1	.	.	.	.	0
0.2	1	1 : 2	.	1	.	.	.	0
0.2	2	1 : 1	1	.	1	.	1	0
0.5	1	1 : 2	1	.	.	.	.	0

sufficient to cause marked headache, flushing and fall in blood pressure.

To make sure that the protective qualities of histamine injections against anaphylactic shock were due to repeated injections and the inferred building up of a tolerance to the drug, three guinea pigs were sensitized to 1 cc. of a 1:10 dilution horse serum. Fourteen days later they received a single dose of 0.2 mg. of histamine. Twenty-four hours later they received 1 cc. of a 1:2 dilution of horse serum intravenously. All the animals promptly developed severe dyspnea and convulsions, and died. The experiment was repeated in three animals with a dose of 0.5 mg. of histamine. They promptly died of anaphylactic shock.

Five guinea pigs were injected with 0.02 mg. of histamine daily for twenty days, and sensitized to horse serum on the sixth day. On the twenty-first day one animal was injected with 4 mg. of histamine. It developed severe dyspnea and convulsions, and died within ten minutes. Three animals received 1 mg. of histamine. Two died from convulsions within twenty-five minutes. The third developed severe dyspnea, and survived. However, when thirty minutes later an intravenous injection of 1 cc. of a 1:5 dilution of horse serum was administered, the guinea pig died in anaphylactic shock. The fifth animal survived the dose of 0.5 mg. of histamine. Twenty-four hours later 1 cc. of a 1:2 dilution of horse serum was administered. It developed moderate dyspnea and slight convulsions, but survived.

Comment.—In guinea pigs weighing 200 to 300 gm., in which a tolerance to small doses of histamine had been developed, a single subcutaneous dose of 1 mg. was poorly tolerated, resulting in death in three of four animals. A single dose of 0.5 mg. of histamine was comfortably tolerated by guinea pigs of such weight. Moderate dyspnea developed after such a dose, both in normal guinea pigs and in those in which an effort was made to build up a histamine tolerance. It may be assumed that the tolerance histamine builds up against itself is relatively limited. Since animals survived shocking doses of horse serum, after the tolerance to histamine had been developed, the amount of histamine released in such animals during anaphylaxis—if any—must be slight.

Histaminase.—Eighteen male guinea pigs of average weight, 200 to 300 gm., were sensitized with an injection of 1 cc. of a 1:10 dilution of horse serum. On the fifteenth day, each animal was injected intravenously with 2 units* of histaminase in 2 cc. of diluent. Fifteen minutes, forty-five minutes, twenty-four hours and forty-eight hours later, the animals received an intravenous injection of 1 cc. of horse serum, 1:2 dilution. Table 4 discloses the results, which show clearly that almost all the animals so treated died promptly in anaphylactic shock.

*One unit of histaminase is the amount which will detoxify 1 mg. of histamine in twenty-four hours, when incubated with it at 37° C.

Seven days were allowed to elapse before the anaphylactic dose of serum was injected intravenously in three animals, who also had been serum-sensitized, and who also had received histaminase on the fifteenth day thereafter, but by the intra-abdominal route. They fared much better, two of the three surviving.

These results are just opposite to those Karady[20] reported with histaminase, using egg white as the antigen. In his series the animals were protected from shock. However, our results with the seven-day group suggested that perhaps histaminase could be of value *in vivo*, if sufficient time were allowed for it to be stored in the tissues, particularly the shock organs. Ac-

TABLE 4

HISTAMINASE GROUP. HORSE SERUM SENSITIZATION, ATTEMPTED PROTECTION WITH HISTAMINASE FROM ANAPHYLAXIS

Time after Histaminase	Number of Animals	Dilution of Horse serum	Dyspnea			Convulsions		Death
			Slight	Moderate	Severe	Slight	Severe	
15 Minutes	8	1:2	1	1	6	.	6	6
45 "	4	1:2	.	.	4	.	4	4
24 Hours	5	1:2	1	.	4	.	4	4
48 "	1	1:2	.	.	1	1	.	0
7 Days (Intra-abdominal)	3	1:2	2	.	1	.	1	1

cordingly, the following experiment to test this new concept was devised.

Sixteen male guinea pigs, average weight 200 to 300 gm., were divided into two groups. Each group received subcutaneous injections of histaminase daily, in 0.2 and 2 unit strengths, for six days, at which time all animals were sensitized to horse serum. In one group the histaminase injections were stopped. In the other they were continued for fourteen days more. In a third group of four animals, sensitization to horse serum was effected and then 0.2 units of histaminase was injected subcutaneously every other day for six doses.

The results in Table 5 show the apparent protective value of histaminase injections against anaphylactic shock.

Of seventeen animals, two died from anaphylaxis—approximately 12 per cent. This was much less than the control group

of 74 per cent. The animals suffered less dyspnea, twitchings and severe convulsions than the histamine-treated group.

In all our experiments, we were acting upon the assumption, true or false, that histamine was the substance released during anaphylaxis, and was responsible for the symptoms produced. Theorizing that a tolerance to this drug could be built up in the shock organs by successive injections, and anaphylaxis thereby prevented, we performed the experiments reported above. Furthermore, we assumed that histaminase, which detoxifies histamine in the test tube, may also be capable of doing so in the body. The results of our experiments suggested that,

TABLE 5

HISTAMINASE GROUP. SERUM SENSITIZED; PROTECTION AGAINST ANAPHYLAXIS BY DAILY INJECTIONS

Histaminase Dosage	Number of Animals	Dilution of Horse Serum	Dyspnea			Convulsions		Death
			Slight	Moderate	Severe	Slight	Severe	
0.2 unit 6 days	3	1 : 7.5	1	.	1	.	1	1
0.2 unit 20 days	1	1 : 7.5	1	.	.	.	.	0
	1	1 : 5	.	1	.	1	.	0
	2	1 : 2	1	.	1	2	.	0
	1	1 : 1	.	.	.	.	.	0
2 units 6 days	2	1 : 2	2	.	.	1	.	0
2 units 20 days*	2	1 : 1	.	.	2	1	.	0
0.2 unit after sensitization 6 doses	1	1 : 1	.	.	.	.	.	0
	4	1 : 2	1	1	2	.	1	1

* Three animals in this group died on the 12th, 18th and 19th days, respectively, from the large doses of histaminase, which in all four animals caused local indurated masses to form at the site of injections, and a loss of weight.

if the substance is given a chance to become stored in the body—presumably in the shock organs—it will protect against anaphylaxis.

Karady[20] has reported that histaminase intravenously protects against both *histamine shock* and *anaphylactic shock*. We injected two guinea pigs with two units of histaminase intravenously. Fifteen minutes later 1 mg. of histamine was injected intra-abdominally. Both animals died from histamine shock in fifteen minutes. Three guinea pigs were then sensitized to horse serum. Fourteen days later each was injected with 2 units of histaminase intravenously. Fifteen minutes

later, 0.5 mg. of histamine was injected intra-abdominally. Normally, this dose is not fatal to guinea pigs. Within fifteen minutes, moderate dyspnea began, lasting for several hours. Twenty-four hours later 1 cc. of a 1:2 dilution of horse serum was injected intravenously. All animals died promptly of anaphylactic shock.

Four guinea pigs were sensitized to horse serum. At the same time, subcutaneous injections of histaminase in 0.2-unit doses were administered, six injections, every other day, totaling 1.2 units. On the fourteenth day 1 mg. of histamine was injected intra-abdominally. In two animals nothing happened. A third developed moderate dyspnea after twenty minutes, but survived. The fourth developed severe dyspnea after twenty-seven minutes and died in convulsions in thirty-five minutes. The injections of histaminase over fourteen days apppeared to protect three out of four animals against histamine shock. In the four controls, three died immediately from a single injection of 1 mg. of histamine.

The three guinea pigs who survived the above experiment received an intravenous injection of 1 cc. of a 1:2 dilution of horse serum twenty-four hours after the histamine injection. All three animals promptly developed anaphylactic shock and died in convulsions. It will be noted in Table 5 that, of four animals similarly treated but who had been spared the histamine injection, three failed to develop anaphylactic shock. The apparent conclusion, that the histaminase was used up in detoxifying the histamine and thus was not available to protect against anaphylaxis, requires further investigation.

Discussion of Experimental Work.—It would appear that histamine and histaminase are capable of protecting against anaphylactic shock in guinea pigs. Histamine injections apparently build up a tolerance on the part of the organism to histamine. This tolerance renders the shock organs refractory to histamine, the substance that has been presumed by many investigators[12, 13, 14] to be released during anaphylaxis. However, the tolerance is limited.

It appears from our experiments that histaminase protects against anaphylaxis and histamine shock in guinea pigs. Furthermore, very little histaminase is required for this purpose. Best and McHenry[1] found that histaminase takes

twenty-four hours to detoxify histamine in a test tube. From our work it could be argued that histaminase was capable of acting at once in the guinea pig.

However, our clinical experience tells a different story.

CLINICAL EXPERIENCE

In twelve cases of *asthma*, four of *vasomotor rhinitis* and four of *urticaria*, enteric-coated tablets of histaminase were prescribed.

In all the cases a detailed history was taken and careful physical examination performed. The patients were subjected to a thorough allergic investigation. Skin tests, *x*-rays of chest and sinuses, blood and other laboratory data were secured. Most of the cases were of long duration and had received previous treatment, generally with a measure of relief. There were eight males and twelve females. With the exception of one child, all were adults. All were members of the white race. One experienced a gastro-intestinal upset after two doses of 15 units each.

These patients were requested to keep an accurate and complete record of their symptoms and to note daily whether or not any improvement was observed. The group was very cooperative. All were eager to obtain relief and, if anything, might have been more apt to exaggerate the good results rather than the bad.

Bronchial Asthma.—Contrary to reports in the literature, our clinical results with the oral administration of histaminase in bronchial asthma were sadly disappointing. We append, herewith, a brief protocol of the individual cases:

Case I.—V. S., white, male, aged thirty-one. Bronchial asthma for two and a half years with two or three attacks weekly. By intracutaneous tests he was found markedly positive to sweet potato and chocolate, and moderately positive to house dust, asparagus, peaches, ragweed and yeast. The attacks were perennial. Partial relief was obtained by use of ephedrine and weekly immunizing injections of house dust and yeast. Nevertheless, a severe cough, mild dyspnea and wheezing were present at all times. Five units of histaminase were given t.i.d. for two weeks, without relief. The dose was then increased to 10 units t.i.d. for three weeks, with no relief. The dose was now increased to 30 units t.i.d. for two more weeks, with no relief. The wheezing, cough and heavy breathing still persisted.

Case II.—L. S., white, male, aged seven. Son of previous patient. Asthma for six years with attacks once weekly. Skin tests disclosed a mod-

erate reaction to dust, tomato, rice, fish glue, pyrethrum, Hormodendron and Penicillium. Restriction of diet, in addition to dust and vaccine injections, rendered considerable relief from acute attacks, although the wheezing and heavy breathing still occurred on occasions, the attacks taking place about once every two months. Histaminase was prescribed, 10 units t.i.d. for two weeks, but gave no relief, the wheezing continuing. Twenty units t.i.d. appeared to help somewhat during the third week, the wheezing disappearing. However, during the fourth and fifth weeks the wheezing and dyspnea were no better. An upper respiratory infection during the fifth week precipitated an asthmatic attack, despite the use of histaminase.

Case III.—N. R., white, female, aged twenty-four. Asthmatic attacks for five years occurring approximately every two to three days. Adrenalin was usually required for relief. The skin was only slightly sensitive to dust and lemon. An eosinophilia of 16 per cent was present. Considerable expectoration was raised daily. Patient improved upon the administration of an autogenous vaccine. Although attacks continued, they were not as severe or as long in duration. Histaminase was prescribed, 5 units t.i.d. Slight improvement occurred during the first two weeks, but it was not very marked. Fifteen units of histaminase t.i.d. then were given for three weeks. During this time two attacks occurred. Finally, 30 units t.i.d. were given for another two weeks. No improvement was noted.

Case IV.—R. E., white, female, aged forty-five. Asthmatic attacks for fifteen years, occurring about once every week. Intradermal skin tests showed a marked reaction to house dust, horse epithelium, and goat epithelium, and a moderate reaction to orris root, white potato, chicken, cabbage and tobacco. Dust and vaccine injections had reduced the frequency of attacks. Wheezing and dyspnea and occasional milder asthmatic attacks persisted. Five units of histaminase were prescribed for three weeks and at first the patient thought it helped, because the attacks had become less severe. Histaminase, at 5-unit dosage t.i.d., was continued for another three weeks. During these three weeks the patient had numerous attacks. The histaminase was increased to 30 units t.i.d. There was no change in the symptomatology. If anything, the patient was worse while taking the histaminase.

Case V.—J. F., white, female, aged sixty. Severe asthmatic attacks for three years. Skin tests disclosed moderate reactions to dust and duck. There was a 4 per cent eosinophilia. Potassium iodide gave this patient considerable relief. Dust and vaccine injections did not augment this much. Bronchial rales, with occasional dyspnea and wheezing, continued. Damp and rainy weather occasionally precipitated an acute sinusitis and an attack of asthma. Histaminase, 5 units t.i.d., was prescribed. For two weeks the patient thought that she felt better. The dosage was increased to 15 units t.i.d. for four weeks. The patient began to wheeze and the occasional attacks returned. The dosage was increased to 30 units t.i.d. for the next two weeks, but the patient still obtained no relief from dyspnea, wheezing or the acute attacks.

Case VI.—J. A., white, male, aged sixty. Asthmatic attacks for eleven years, several times a week, requiring hypodermic injections of epinephrine for relief. All skin tests were negative. No focus of infection was discovered. All laboratory tests were negative. The patient was apparently in excellent physical condition with the exception of asthma. All known ther-

apeutic measures were tried without success. Histaminase, 15 units t.i.d., was prescribed for four weeks, but no change in the condition was noted.

Case VII.—A. C., white, male, aged twenty-eight. Has suffered from frequent attacks of asthma for sixteen years. His skin tests showed a sensitivity to house dust, beef, coffee, timothy and ragweed. The attacks were perennial. Some relief was obtained from dust and ragweed injections, but wheezing and occasional attacks persisted. Histaminase in 15-unit doses t.i.d. was tried for four weeks. No relief whatsoever was obtained.

Case VIII.—A. B., white, female, aged twenty-eight. Asthma for one year without any previous treatment. Skin tests disclosed marked reactions to horse epithelium and codfish, and moderate reactions to house dust, lemon, shrimp and chicken. Histaminase in 15-unit doses t.i.d. was given for four weeks without any relief.

Case IX.—H. B., white, male, aged fifty-four. Bronchial asthma and emphysema. Has infected sinuses. Skin tests negative. Blood eosinophilia 6 per cent. Sputum examination discloses hemolytic Staphylococcus aureus. Histaminase, 15 units t.i.d., was prescribed for six weeks, with no benefit whatsoever.

Case X.—J. W., white, female, aged thirty-two. Bronchial asthma for the past seven years. Attacks occurred on the average of four or five times a week requiring epinephrine hypodermically. The patient was sensitive to dust and feathers. Both antrums were infected. The patient was free from attacks in Arizona; she had just returned and asthmatic attacks were as frequent as before when histaminase, 15 units t.i.d., was prescribed. The dose was increased to 30 units t.i.d. after second week for four additional weeks. No relief from severity, duration or frequency of attacks was obtained.

Case XI.—D. B., male, aged fifty. Asthma for over twenty years. Tested intradermally on several occasions but all tests were negative. The patient had undergone sinus surgery three years ago. He has been receiving vaccine treatments for the past two years but still wheezes and has considerable dyspnea. Epinephrine, orally and hypodermically, has been necessary at least two or three times weekly. Histaminase, 30 units t.i.d., was prescribed for six weeks, but there was no relief from symptoms. The patient still has to resort to epinephrine injections.

Case XII.—S. R., female, aged thirty-six. Bronchial asthma for seven years. The patient is sensitive to ragweed and dust, and has an infected right antrum. Attacks used to occur two or three times weekly throughout the year. Epinephrine was required for relief. The patient received some benefit from ragweed and dust inoculations but still has weekly attacks. Histaminase, 15 units t.i.d., was prescribed for six weeks, but had no influence on the attacks, which still occurred as often and as severely as before.

Vasomotor Rhinitis.—The results in our cases of vasomotor rhinitis likewise were poor:

Case XIII.—L. J., white, female, aged thirty-six, school teacher. Vasomotor rhinitis for over twelve years. The patient is sensitive to timothy and

dust, with symptoms persisting throughout the year. Histaminase, 15 units t.i.d., was prescribed. Marked relief was obtained, but this cannot be ascribed to the histaminase since this patient also began to receive timothy and autogenous dust inoculations at the same time.

Case XIV.—H. G., white, male, aged twenty-one. Vasomotor rhinitis for ten years. Within the past two years the patient has had a turbinectomy, polypiectomy and radical antrum operation performed, without any relief. Skin tests disclose a moderate reaction to house dust, sweet potato and rice. Patient was placed on histaminase, 15 units t.i.d., for one week, without relief. For the second week the dose was increased to 30 units t.i.d., and the patient thought he felt some relief during the day but none at night. During the third week, however, he felt quite certain he was obtaining no relief whatsoever. Histaminase was discontinued.

Case XV.—A. L., white, female, aged twenty-six. Vasomotor rhinitis for the past six or seven years. Skin tests negative. Ten per cent eosinophilia present. A nasal smear disclosed numerous clumps of eosinophils. Histaminase was prescribed, but 15 units t.i.d. for two weeks gave no relief. The dosage was increased to 30 units t.i.d. No relief was obtained after four weeks' additional treatment.

Case XVI.—L. B., white, male, aged forty, jeweler. Vasomotor rhinitis for past ten or twelve years. All skin tests were negative with exception of dust. Histaminase was prescribed, 10 units t.i.d., for two weeks, then increased to 15 units for three weeks more. No relief from symptoms was obtained.

Urticaria.—The results in urticaria were not encouraging:

Case XVII.—R. C., white, female, aged twenty-four. Attacks of urticaria following ingestion of fish. Histaminase, 15 units t.i.d., was prescribed immediately upon onset of symptoms, and the lesions disappeared within three days. It should be noted that this may have occurred without the administration of the histaminase, since the disturbing allergen was known and was immediately withdrawn from the patient's diet upon the onset of symptoms.

Case XVIII.—H. W., female, aged forty-four. Angioneurotic edema of unknown origin. All skin tests were negative, and elimination diets were of no avail. The attacks occurred almost daily, affecting the lips and eyes. Histaminase, 15 units t.i.d., was prescribed for six weeks. No relief whatsoever was obtained.

Case XIX.—B. D., white, female, aged thirty-eight. Frequent attacks of angioneurotic edema for over a year. The usual sites of election were the eyes, lips and tongue. For the past three months, the tongue had been swelling two or three times a week. Physical examination and all laboratory tests were negative. No foci of infection were found. Intradermal skin tests were negative. Six per cent eosinophilia was present. Histaminase was prescribed, 15 units t.i.d., for two weeks, increased to 30 units t.i.d. for the succeeding three weeks. No relief was obtained.

Case XX.—H. L., white, female, aged twenty-four. Urticaria for three weeks, with no clue as to cause. Skin tests were negative. Histaminase was prescribed, 15 units t.i.d. After two doses the patient experienced a severe gastro-intestinal upset. The histaminase was discontinued.

Comment.—There may be a number of reasons why our clinical results with histaminase were so poor.

We might very easily, on the basis of the successful prevention of anaphylaxis in guinea pigs by histaminase administered by the parenteral route, attribute our failure in humans to the difference in the method of administration. There are instances in medicine in which drugs, effective by the parenteral route, are ineffective by the enteral route. Perhaps the enteric coating of the histaminase tablets was digested or dissolved off within the gastro-intestinal tract, following which that part of the material which was protein in nature may have undergone disintegration in the process of digestion. Then, too, the enteric coating may have resisted all solution and thus prevented absorption of the histaminase. Thirdly, the material —if absorbed at all—may have been absorbed in insufficient quantity to be of any value. A fourth explanation may be that the substance, though completely absorbed, was excreted too rapidly. Finally, despite the claims of some investigators, histamine may not be the cause of allergic phenomena in humans, and therefore its detoxification by histaminase is of no significance.

For our part, it is sufficient to note that in twenty allergic individuals the results were extremely poor. In fact, in only one case—that of an urticaria caused by the indigestion of fish—was there complete relief. Even here there is a strong probability that the urticaria would have cleared up simply by eliminating the offending allergen.

CONCLUSIONS

1. Experimentally, the administration of histaminase appeared to protect guinea pigs against anaphylaxis and histamine shock.

2. Clinically, the oral administration of histaminase was of no value in treating twenty cases of bronchial asthma, vasomotor rhinitis and urticaria.

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